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Adrenaline Reaction in Diabetes Mellitus

By

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The production of hyperglycemia and glycosuria following the injection of adrenaline was demonstrated by Blum[1] (1901) and since then the procedure has been utilized as a test for liver function by many authors at home and abroad.[2)-9)]

In our Clinic also, Sakamaki[10] and Okubo[11] recognized the value of this procedure in a biological and a clinical test, respectively.

On the other hand, the liver is inseparably linked up with carbohydrate metabolism, consequently, with diabetes mellitus. The significance of adrenaline response in diabetes mellitus, therefore, is thought to be unusually great.

In this paper I attempted to study the blood sugar curves after adrenaline injection in diabetes mellitus.

Experimental

Method

Examinations were performed in 37 cases of diabetes mellitus, containing 15 cases of Type I and 22 of Type II.[12)13)] One case of renal glycosuria and 4 cases of healthy person were also investigated.

The patients received no food nor insulin after supper the previous evening and the test was performed the following morning.

In each subject 0.5 cc. of adrenaline solution (=0.5 mg.) were injected subcutaneously. The blood sample was taken from the ear lobe before adrenaline injection and at every 30 minutes for 5 hours after injection. The urine sugar was also examined every one hour.

The blood sugar was estimated by Fujita-Iwatake's method,[14)] and the urine sugar by Bertrand's method.[15)]

Results

The data are given in Table I, of which typical curves from each type are shown in Figs. 1 and 2.

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Fig. 1

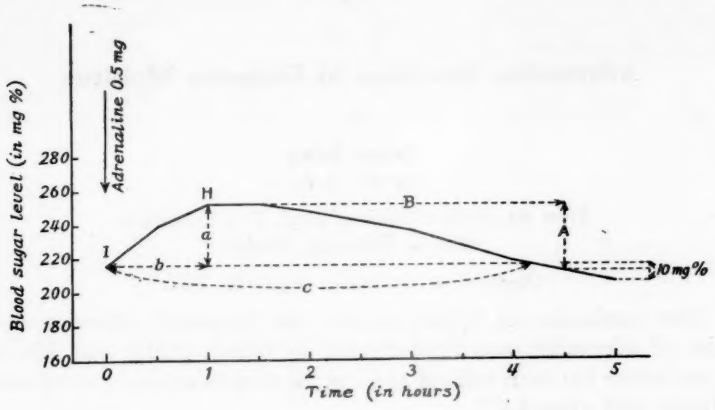

Fig. 2

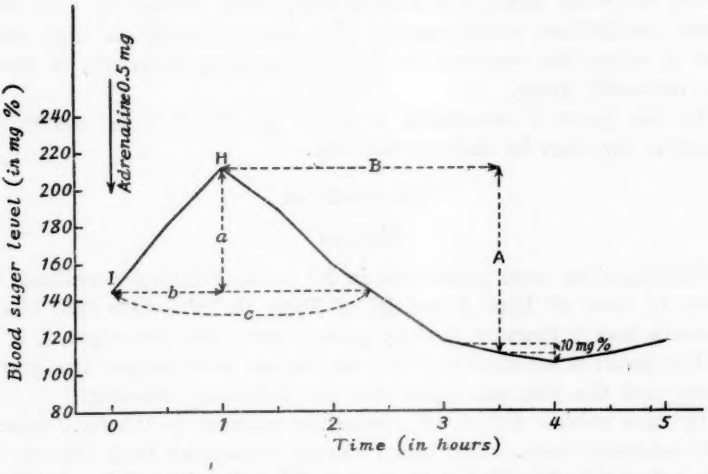

Fig. 1. Example of the blood sugar curve after adrenaline injection in Type II. Case No. 16.

a=35 . . . . . Magnitude of hyperglycemia (mg.%). b=1 . . . . . Hyperglycemic time (hours). c=4 1/6 . . . . . Recovery time (hours). H/I=1.16 . . . . . Hyperglycemic index. A/B=13.0 . . . . . Adrenaline depression quotient.

Fig. 2. Example of the blood sugar curve after adrenaline injection in Type I. Case No. 27.

a=66. b=1. c=2 1/3. H/I=1.46. A/B=40.0.

TABLE I

Total Cases

Type	No.	Sex	Age	Blood sugar before and after insulin injection (mg.%)											Urine sugar in 5 hours (g.)
				Initial blood sugar	30′	1°	1°30′	2°	2°30′	3°	3°30′	4°	4°30′	5°	
Type II	1	♂	42	404	425	449	416	374	357	301	291	277	259	252	25
	2	♂	31	371	379	403	409	389	381	367	352	346	346	360	46
	3	♂	46	306	343	359	371	338	284	282	291	266	266	259	18
	4	♂	50	304	353	353	347	334	330	311	306	303	303	296	58
	5	♂	14	302	326	382	374	358	356	354	328	314	298	292	15
	6	♂	45	294	358	382	368	358	340	304	278	278	278	274	6
	7	♂	45	282	320	352	346	329	313	306	289	271	258	249	11
	8	♂	37	280	292	314	317	312	296	287	285	283	268	265	12
	9	♀	26	255	321	367	372	360	325	303	276	255	245	229	6
	10	♂	65	250	292	307	297	282	268	260	248	240	231	220	7
	11	♂	52	245	291	286	274	255	241	234	217	207	191	205	5
	12	♀	42	238	277	295	293	270	252	245	227	197	191	166	6
	13	♂	38	236	260	274	262	240	230	218	210	188	182	178	1
	14	♂	63	236	271	298	298	281	275	265	252	238	226	214	4
	15	♀	16	230	258	256	251	245	233	207	204	181	174	165	3
	16	♂	60	216	238	251	251	247	242	237	228	218	212	204	0.2
	17	♀	62	184	235	259	242	231	209	188	169	155	164	170	2
	18	♂	60	178	207	252	255	238	222	198	179	164	152	139	9
	19	♀	69	160	204	235	225	209	193	178	172	157	151	146	0.1
	20	♂	43	158	197	211	211	210	203	197	188	186	183	163	0
	21	♀	25	132	233	244	221	212	171	151	130	118	117	120	0
	22	♂	57	111	134	181	165	150	117	131	115	113	120	108	0
Type I	23	♂	39	260	287	303	306	301	295	285	267	255	242	223	6
	24	♀	56	175	184	228	244	233	213	183	167	149	132	127	2
	25	♂	44	153	160	211	228	231	231	202	174	164	132	127	3
	26	♀	64	150	178	221	209	172	155	144	136	124	120	117	0
	27	♂	50	145	181	211	190	159	139	118	111	106	111	117	2
	28	♂	69	129	177	211	207	178	152	134	118	108	100	103	0
	29	♂	55	118	164	205	193	162	118	101	91	70	73	77	0.3
	30	♀	36	118	214	235	188	144	111	88	87	92	97	99	1
	31	♂	63	113	151	164	159	134	114	108	99	94	91	103	0
	32	♂	55	111	145	143	130	106	99	101	96	104	113	103	0
	33	♂	63	98	169	162	141	120	99	92	87	87	89	88	0
	34	♂	45	87	136	144	121	95	85	83	90	91	89	92	0
	35	♀	21	85	110	125	100	92	84	86	90	92	87	84	0
	36	♂	46	80	132	108	89	84	71	73	75	78	—	—	0
	37	♀	20	78	127	141	9?	52	63	66	61	—	70	71	0
Renal glycosuria	88	♂	30	77	167	136	87	64	59	80	78	89	94	103	1
Healthy person	39	♂	28	104	178	184	151	109	92	70	93	88	94	95	0
	40	♂	27	94	165	146	108	84	80	75	85	91	89	92	0
	41	♂	25	89	181	179	141	113	79	63	72	82	92	94	0
	42	♀	26	75	148	138	99	71	70	59	56	82	78	80	0

The magnitude of hyperglycemia, which is shown by the difference between the prime blood sugar value before adrenaline injection and the maximum value after the injection, ranges from 117 to 28 mg.% in Type II, and from 117 to 34 mg.% in Type I. It shows the normal

value in the large majority of cases in both Types (Table II).

The hyperglycemic time, at which the blood sugar reaches its maximum, ranges from ½ to 1½ hours in Type II and from ½ to 2 hours in Type I (Table II).

TABLE II

Varieties of Criteria Measured from the Curves

Type	No.	Sex	Age	Initial blood sugar value (mg.%)	Magnitude of hyperglycemia (mg.%)	Hyperglycemic time	Recovery time	Hyperglycemic index	Adrenaline depression quotient
Type II	1	♂	42	404	45	1°	1°40′	1.11	54.3
	2	♂	31	371	38	1°30′	2°50′	1.10	28.5
	3	♂	46	306	65	1°30′	2°20′	1.21	42.0
	4	♂	50	304	49	30′	3°40′	1.16	16.7
	5	♂	14	302	80	1°	4°20′	1.26	24.0
	6	♂	45	294	88	1°	3°10′	1.30	41.5
	7	♂	45	282	70	1°	3°40′	1.25	26.9
	8	♂	37	280	37	1°30′	4°10′	1.13	16.3
	9	♀	26	255	117	1°30′	4°	1.46	40.9
	10	♂	65	250	57	1°	3°30′	1.23	21.8
	11	♂	52	245	46	30′	2°20′	1.19	25.0
	12	♀	42	238	57	1°	3°10′	1.24	32.3
	13	♂	38	236	38	1°	2°10′	1.16	26.3
	14	♂	63	236	62	1°15′	4° 5′	1.26	24.0
	15	♀	16	230	28	30′	2°35′	1.12	21.0
	16	♂	60	216	35	1°15′	4°10′	1.16	13.0
	17	♀	62	184	75	1°	3° 5′	1.41	34.7
	18	♂	60	178	77	1°30′	3°30′	1.43	33.1
	19	♀	69	160	75	1°	3°50′	1.47	24.0
	20	♂	43	158	53	1°	5°	1.34	13.7
	21	♀	25	132	112	1°	3°30′	1.85	42.0
	22	♂	57	111	70	1°	4°50′	1.63	26.4
Type I	23	♂	39	260	46	1°30′	3°50′	1.18	23.7
	24	♀	56	175	69	1°30′	3°10′	1.39	37.3
	25	♂	44	153	78	2°	4°10′	1.51	49.5
	26	♀	64	150	71	1°	2°40′	1.47	32.3
	27	♂	50	145	66	1°	2°20′	1.46	40.0
	28	♂	69	129	82	1°	3°10′	1.64	34.3
	29	♂	55	118	87	30′	2°30′	1.74	45.6
	30	♀	36	118	117	1°	2°25′	1.99	73.5
	31	♂	63	113	51	1°	2°30′	1.45	26.0
	32	♂	55	111	34	30′	1°50′	1.31	23.0
	33	♂	63	98	71	30′	2°35′	1.72	30.8
	34	♂	45	87	57	1°	2°25′	1.66	39.3
	35	♀	21	85	40	1°	2°30′	1.47	33.0
	36	♂	46	80	52	30′	2°10′	1.65	30.5
	37	♀	20	78	63	1°	1°40′	1.81	89.0
Renal glycosuria	38	♂	30	77	90	30′	1°40′	2.17	68.7
Healthy persons	39	♂	28	104	80	1°	2°10′	1.77	57.0
	40	♂	27	94	71	30′	1°50′	1.76	54.0
	41	♂	25	89	92	30′	2°20′	2.03	47.2
	42	♀	26	75	73	30′	1°55′	1.97	35.6

The recovery time, at which the blood sugar reaches its prime starving level, ranges from 1 2/3 to 4 1/6 hours in Type I (Table II).

The hyperglycemic time and the recovery time show variations from the normal value in the majority of cases.

The hyperglycemic index, which corresponds to the quotient of the maximum blood sugar value after adrenaline injection (H) and the prime fasting blood sugar value (I), ranges from 1.11 to 1.85 in Type II and from 1.31 to 1.99 in Type I (Table II, Figs. 1 and 2).

Furthermore, I contrived a new quotient to show the velocity of the blood sugar depression after arriving at its maximum following adrenaline injection (Figs. 1 and 2). First the difference between the maximum blood sugar value after adrenaline injection and the minimum following it were measured (A), and then the interval between both times, at which the above blood sugar levels occurred respectively were measured (B).

At this juncture, due consideration was given for the selection of the minimum blood sugar levels.

For the same reason as stated in the previous paper,[16] I regarded as the minimum value the blood sugar level, which came first within 10 mg.% above the lowest level shown on the curve.

Thus the quotient of A and B was calculated as the adrenaline depression quotient.

The adrenaline depression quotient ranges from 13.0 to 54.3 in Type II and from 23.7 to 73.5 in Type I (Table II).

Concerning the magnitude of hyperglycemia, the hyperglycemic time and the recovery time, no significant difference was seen between both types of diabetes (Table III).

On the contrary, the hyperglycemic index and the adrenaline depression quotient revealed significant difference between both types (Table III).

TABLE III

Differences between Diabetic Types

Criteria	Remarks	Type I	Type II	x_c^2
Magnitude of hyperglycemia	Above 51 mg.% Below 50 mg.%	12 3	14 8	0.49
Hyperglycemic time	Above 1°15′ Below 1°	3 12	7 15	0.17
Recovery time	Above 2°30′ Below 2°25′	9 6	18 4	1.19
Hyperglycemic index	Above 1.30 Below 1.29	14 1	8 14	9.76*
Adrenaline depression quotient	Above 30 Below 29	12 3	8 14	5.19*

Highly significant difference in the hyperglycemic index, for the

most part, may be due to difference in initial blood sugar level, which participated in this index as its denominator.

Significant difference in the adrenaline depression quotient, reveals the fact that the velocity of the recovery from adrenaline-induced hyperglycemia delays markedly in Type II.

To observe the adrenaline-induced extra-glycosuria I estimated the balance between the doses of urine sugar excreted actually in the course of 5 hours after adrenaline injection, and that which is calculated from the percentage of the prime urine sugar before injection multiplied by the doses of urine in the course of 5 hours after the injection.

The results are shown in Table IV and V. In addition to the cases included in the Table V, especially in Type I though not shown in the table, the urine sugar is absent before and after the injection in 9 cases, 2 of which show the hyperglycemia above 200 mg.% after the injection.

An elevation of the renal threshold for glucose after adrenaline injection seems to occur in the majority of diabetes mellitus.

Furthermore, there is no close relation between the adrenaline-induced hyperglycemia and the blood pressure (Table VI).

Discussion

There is a divergence in opinions on the adrenaline response in diabetes mellitus, according to various methods.[17)-20)]

In the present work also the adrenaline response shows the normal value in the majority of cases, concerning the magnitude of hyperglycemia.

On the contrary, concerning the hyperglycemic time and the recovery time, it shows variations from normal value in the majority of cases.

Concerning the difference between both types of diabetes mellitus, it was found that in Type II the hyperglycemic index diminishes, which was explained by the increase in its initial blood sugar, a component of this index. Therefore, this index is inadequate as criteria for the estimation of adrenaline reaction in diabetes mellitus.

Adrenaline depression quotient, which was designed to show a velocity of recovery from adrenaline-induced hyperglycemia, revealed highly significant difference between both Types.

These results suggest that in diabetes mellitus, especially in severe cases, doses of endogenous insulin secreted following the injection of adrenaline are insufficient and the sensitivity of tissue to the adrenaline diminishes.

In 1924, Kylin[21)] stated that adrenaline-induced hyperglycemia was low in diabetes mellitus associated with hypertension, and high in diabetes

TABLE IV

Extra Urine Sugar Induced by Adrenaline

Type	No.	Urine sugar in 5 hours (g.)	Express of urine sugar (g.)
Type II	1	25	?
	2	46	+ 2.64
	3	18	−10
	4	58	− 2
	5	15	− 3
	6	6	?
	7	11	− 2
	8	12	+ 0.2
	9	6	− 2
	10	7	− 2
	11	5	− 2
	12	6	+ 0.2
	13	1	− 3
	14	4	+ 3
	15	3	− 1
	16	0.2	− 1
	17	2	+ 1
	18	9	+ 3
	19	0.1	+ 0.1
	20	0	− 2
	21	0	—
	22	0	—
Type I	23	6	− 0.4
	24	2	+ 2
	25	3	+ 3
	26	0	—
	27	2	+ 2
	28	0	—
	29	0.3	+ 0.3
	30	1	+ 1.3
	31	0	—
	32	0	—
	33	0	—
	34	0	—
	35	0	—
	36	0	—
	37	0	—
Renal glycosuria	38	1	+ 1
Healthy persons	39	0	—
	40	0	—
	41	0	—
	42	0	—

mellitus without hypertension, classifying diabetes in two types from this viewpoint.

My results fail to verify this conception.

CONCLUSIONS

1. In order to observe the adrenaline reaction in diabetes mellitus,

the blood sugar curves after subcutaneous adrenaline injection were studied in 15 cases of Type I and 22 of Type II.

2. Concerning the magnitude of hyperglycemia, the adrenaline reaction shows the normal value in the majority of cases.

3. Concerning the hyperglycemic time and the recovery time, the adrenaline response shows variations from normal value in a large majority of cases.

TABLE V

Differences of Extra Sugar between Both Diabetic Types

Type	Excess of urine sugar	
	+	−
II	7	11
I	5	1
Renal glycosuria	1	

TABLE VI

Relation between Adrenaline-induced Hyperglycemia and Blood Pressure

Blood pressure (max.) (mm.Hg.)	Magnitude of hyperglycemia (mg.%)		
	31—50	51—80	81—120
Above 151	2	4	1
150—111	4	10	4
Below 110	2	3	2

4. As criteria for the estimation of adrenaline reaction the adrenaline depression quotient was newly measured, which showed the velocity of the recovery from adrenaline-induced hyperglycemia. By means of this quotient the difference of both types was revealed significantly.

5. Elevation of the renal threshold for glucose after adrenaline injection appears to occur in the majority of diabetes mellitus.

6. There is no close relation between the adrenaline-induced hyperglycemia and the blood pressure.

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The Combined Abdominal and Right Thoracic Approach to Carcinema of the Middle and Upper Thirds of the Esophagus, and its Immediate Results

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The prevailing method for the surgical approach for esophageal carcinoma seems to be the method to bring up the stomach from the left thorax through the left thoracotomy. Lewis (1946),[1] Macmanus (1948),[2] Kent (1950)[3] and others reported a method to bring up the stomach in the right thorax, while Sweet and Garlock (1950)[3] in the United State of America who are the authorities in this field are not in favor to approach the esophageal lesion through the right thoracotomy.

According to our experience, the left thoracotomy for upper and middle esophageal carcinoma seems to be not convenient, because the separation of the tumor behind the aortic arch is hard to perform. Our operative procedure is as follows. 1) Abdominal part: After laparatomy, the stomach is freed. Then the abdominal wall is closed. 2) Chest part: Left thoracotomy is done for lower esophageal carcinoma and cardiac carcinoma. Right thoracotomy is made for upper and middle esophageal carcinoma. Then the tumor is excised and gastroesophageal anastomosis is done. (In both approach the stomach is brought up through the hiatus without dividing the diaphragm.) The abdominal and chest part of this operation is done in one stage.

38 cases of carcinoma of esophagus and cardia have been operated through the chest from April 1950 to September 1952, 3 cases among them died (mortality 7.9%). 16 cases of upper and middle esophageal carcinoma were operated by bringing the stomach through the right chest, among them gastroesophageal anastomosis in the right chest was done in 10 cases; and 1 case died by operation. 6 cases had esophagogastrostomy at the right neck by bringing up the stomach from the right chest. 1 of them complicated with empyema thoracis occurred by necrosis of stomach close to the anastomosis died. 15 gastroesophageal anastomoses were performed in the left thorax after the esophageal lesion was resected without any death. 7 cases had gastroesophageal anastomosis at the left neck subcutaneously by bringing the stomach under the skin anterior to the sternum with one death.

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Influence of Splanchnicotomy or Adrenalectomy upon the Hyperglycemia in Rabbits with Excessively High Body Temperature, Produced by the Combination of Heat-Puncture and High Environmental Temperature

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While the elevation of body temperature by heat-puncture alone has no effect on the blood sugar concentration in rabbits, an excessively high temperature, as 42°C. or higher, effected by combining the heat puncture with high environmental temperature, can bring about a remarkable hyperglycemia.[1)]

A trial was made now to extinguish what a part is played there by the splanchnic nerves and by the adrenal medulla as well.

Experimental

Methods

All the methods, procedures, cautions are fully described in the previous reports from this laboratory.

All the operated rabbits were well surviving for a long time. In each experiment a normal rabbit was always paired with that so operated on, as the control. The heat-puncture was carried out simultaneously, i.e. just successively, on both the animals. The procedure is described in Itikawa.[1)]

High environmental temperature was charged in a special chamber, constructed especially. The temperature there in is to be regulated at will electrically. The bodies of both the rabbits were placed parallel in the chamber, their heads being kept thereout. The animals respirate the air of room temperature. This fact should be into account in criticizing the body temperature variations, etc. on severe heating.

Fujita's method was used for blood sugar determination. Respiration, heart rate and anal temperature were measured. In measuring

the latter the rabbits were taken out from the heating chamber.

Results

16 normal individuals, 10 splanchnicotomized rabbits and 10 adrenalectomized ones, viz. 36 rabbits were experimented on. The operated individuals were used to the heating experiment 63–184 days after the final operation. Two degrees of the environmental temperature, viz. 50° and 60°, were applied. The results with 50° are summarized in Tables I & II, and the others (60°) in Tables III & IV.

On the afternoon of the previous day the preparatory operation, i.e. skull bone perforation and dura mater opening, was carried out on both sets of rabbits, namely operated one and control. No food was given on the morning of the experiment day.

After having taken the control blood samples and body temperature the heat-puncture was conducted on both animals. On puncturing some rabbits excited with movements and struggles but only for a while, then calm. In a few cases the pupils dilated transitorily on one side or both.

In an interval of about two hours some blood samples were taken out and the anal temperature measured. Then the chamber was heated for one and a half hours. Meanwhile the determinations were done from time to time. They were also conducted for some hours after having stopped the heating.

An example illustrates the course of experiment, and all the outcome are summarized in the tabular form.

In all the cases, irrespective whether adrenal operation was done or not, the body temperature increased on the puncture. Before conducting the heating, the anal temperature was 39°–40° against 38°–38.5° of the initial. At this moment the blood sugar was found not a whit different from the initial; the both 0.9–0.11%.

For the 50° heating and the 60° yielded quite different figures, especially re the blood sugar events, the data displayed in Tables I & II and Tables III & IV will be dealt with separately.

50° *Heating* (Cf. Tables I & II).

Body Temperature:

Two hours after conducting the heat-puncture the special heating started and continued for one and a half hours. On heating the body temperature ascended further in both sets of animals, but the hyperthermia was of a larger scale in the group of control animals.* The maxiuum temperature was mean 41.1° in the splanchnicotomized rabbits and 41.5° in the adrenalectomized, while it was 43° & 42° in the controls. 42° was never exceeded in the former, while it was exceeded in 5 cases out of 8 in the latter group. In two cases it was 43.5 °& 44°; they died eventually with the final determination.

EXAMPLE 4. (Experiment 15)

Principal experiment

Rabbit ♂

Date of experiment	Time	Blood sugar mg %	Body temperature °C.	Heart rate per min.	Respiration per min.	Body weight kg.	Heating chamber °C.	Room temp. °C.	Remarks
7. V. '36		R adrenalectomy						1.50	
23. VI.		L adrenalectomy and section of auricular nerves						1.80	
29. X.		Skull bone perforated Dura mater opened						2.10	
30. X.	8:00	99	37.9	46×6	14×6			13	
	8:20	107	37.7	44×6	12×6				
	8:25	Punctured corp. str. bilaterally							After puncture rabbit calm
	9:50	111	38.5	47×6	11×6				
	10:00	Lighted special heating, for 1½ hour							
	10:20	116	39.3	48×6	15×6		52		
	10:50	111	41.3	48×6	17×6		60		
	11:20	116	42.5	52×6	23×6		60	14	Rabbit excited with movements
	11:30	Stopped heating							
	11:50	121	42.4	52×6	30×6				
	12:20	123	40.7	49×6	14×6				
	12:50	143	40.5	48×6	14×6				
	1:20	116	40.0	48×6	13×6				
	2:20	116	39.5	50×6	11×6				
	3:20	114	39.4	48×6	11×6			15	

Control experiment

Rabbit ♂

7. IX.		Section of auricular nerves						1.35	
29. X.		Skull bone perforated Dura mater opened						1.60	
30. X.	7:50	107	38.2	45×6	19×6			13	
	8:10	104	38.2	46×6	13×6				
	8:15	Punctured corpus striatum bilaterally							After puncture rabbit moved
	9:40	109	38.9	49×6	10×6				
	10:00	Lighted special heating, for 1½ hour							
	10:10	102	40.0	48×6	12×6		52		Rabbit salivated, excited
	10:40	109	42.2	54×6	17×6		60		
	11:10	135	43.2	60×6	20×6		60	14	Respiration rapid, dyspnoic
	11:30	Stopped heating							
	11:40	133	43.0	62×6	23×6		45		Heart irregular
	12:10	151	42.5	60×6	20×6				
	12:40	161	42.0	58×6	21×6				
	1:10	154	41.5	59×6	20×6				
	2:10	147	41.0	54×6	20×6				
	3:10	135	40.8	50×6	21×6			15	

As the environmental temperature reduced on having stopped the heating, the body temperature fell gradually, but a higher value was always still noted at the end of determination, viz. 3–4 hours after the dis-

TABLE

Blood Sugar Content and Body Temperature of Doubly puncture and 50° En-

	No. of experiment	Sex	Body weight kg.	Date of experiment	Initial		Before special heating			Maximal blood sugar			At highest body temperature		
					Blood sugar mg%	Body temp. °C.	Blood sugar mg%	Body temp. °C.	Hours after puncture	Blood sugar mg%	Body temp. °C.	Hours from heating	Blood sugar mg%	Body temp. °C.	Hours from heating
Principal experiment	1	♂	2.00	20.X.'36	89	37.9	81	39.0	$1^{11}/_{12}$	106	41.6	$1^{1}/_{3}$	106	41.6	$1^{1}/_{3}$
	2	♀	1.95	30.X.	90	37.3	104	38.5	$1^{5}/_{6}$	105	40.8	$1^{1}/_{2}$	97	41.0	$2^{1}/_{2}$
	3	♂	1.85	8.XII.	81	37.6	85	38.5	$1^{1}/_{2}$	96	40.7	$1^{11}/_{12}$	96	40.7	$1^{11}/_{12}$
	4	♂	1.80	19.XII.	95	38.8	103	40.4	$1^{1}/_{2}$	118	40.7	$1^{11}/_{12}$	93	41.0	$1^{5}/_{12}$
	Mean		1.90		89	37.9	93	39.1	$1^{2}/_{3}$	106	41.0	$1^{2}/_{3}$	98	41.1	$1^{5}/_{6}$
Control experiment	1′	♀	1.75	20.X.'36	100	37.3	103	40.0	$^{11}/_{12}$	166	41.9	3	140	42.6	$1^{1}/_{2}$
	2′	♂	1.65	30.X.	88	38.1	114	40.2	$1^{5}/_{6}$	199	41.9	$3^{1}/_{3}$	143	43.5	$1^{1}/_{2}$
	3′	♀	1.40	8.XII.	98	38.4	108	39.2	$1^{1}/_{2}$	133	41.3	$2^{3}/_{4}$	126	41.7	$1^{3}/_{4}$
	4′	♀	1.65	19.XII.	105	39.8	111	41.0	$1^{1}/_{2}$	164	41.2	$1^{3}/_{4}$	118	44.0	$^{3}/_{4}$
	Mean		1.61		98	38.4	109	40.1	$1^{1}/_{2}$	166	41.6	$2^{2}/_{3}$	132	43.0	$1^{3}/_{8}$

continuance of heating.

Blood Sugar:

Hyperglycemia was also of a greater degree in the control animals. The content was mean 0.17% (0.13–0.2%) and 0.15% (0.13–0.55%), while it was mean 0.11% (0.1–0.12%) in the splanchnicotomized individuals and 0.12% in the adrenalectomized ones. The period of hyperglycemia was accordingly much longer in the control animals, 1–3 hours being noted. The peak of hyperglycemia appeared commonly 1–2 hours later than that of body temperature.

60° *Heating* (Cf. Table III & IV).

Body Temperature:

The maximum anal temperature in the operated animals in the 60° chamber was 43° (42.4°–43.6°) in the splanchnic otomized rabbits and also in the adrenalectomized (42.5°–42.9°). It was in the control animals 44° and 43°. Commonly the last determination in the chamber was the highest. In two cases (9′, 12′) the temperature above 44° was observed,

I

Splanchnicotomized Rabbits and the Normal on Heat-
vironmental Temperature

At highest environmental temp.			Blood sugar when body temperature at 40°C.	Heart rate per min.	Frequency of respiration per min.	Special heating °C.	Room temperature °C.	Splanchnicotomy	
Blood sugar mg%	Body temp. °C.	Hours from heating						Date	Body weight
105	41.0	5/6	86	216–276	48–120	45–55	11–20	22. VII.	1.60
105	40.8	1 1/2	92	270–312	48– 66	50–55	11–14	23. VII.	1.40
91	40.4	1 5/12	93	240–288	48–102	50–53	9–16	1. X.	1.80
93	41.0	1 5/12	100	288–378	60–196	45–50	15–18	8. X.	1.85
99	40.8	1 1/3	93	254–314	51–121	48–53	12–18		1.66
120	41.5	1	90	224–324	66–198	46–55	11–20		
143	43.5	1 1/2	114	288–384	60–168	50–55	11–14		
116	41.3	1 1/4	113	272–360	72–270	50–53	9–16		
144	42.4	1 1/4	110	240–408	84–144	48–50	15–18		
131	42.2	1 1/4	107	257–369	71–195	49–53	12–17		

the death occurred 1 to 1.5 hours thereafter. The other animals survived well or died on the night of the experiment day. At the end of experiment, viz. 3–4 hours after discontinuation of heating the body temperature did not yet recover.

Blood Sugar:

All the animals were warm as high as 42, at least, and a heavy hyperglycemia developed therein, even in the animals, interfered with the medulli-adrenal function. Its acme was 0.14% (0.12–0.16%) in the splanchnicotomized and also in the adrenalectomized (0.13–0.14%). 0.15% and 0.17% were the mean values of their controls.

It is clearly known from the sugar data, the hyperglycemia in the control experiments was of quite the same magnitude in both sets of heating, i.e. of 50° & 60,° while the hyperglycemia estimated in the rabbits, deprived of either splanchnic nerves or the adrenals was distinctly smaller in the chamber of 50° than in that of 60.° 0.11% against 0.14%. And the latter was distinctly smaller than that of control animals of both sets;

TABLE

Blood Sugar Content and Body Temperature of Doubly Heat-puncture and 50°

	No. of experiment	Sex	Body weight	Date of experiment	Initial		Before special heating			Maximal blood sugar			At highest body temperature		
					Blood sugar mg%	Body temp. °C.	Blood sugar mg%	Body temp. °C.	Hours after puncture h.	Blood sugar mg%	Body temp. °C.	Hours from heating h.	Blood sugar mg%	Body temp. °C.	Hours from heating h.
Principal experiment	5	♂	1.85	11.X.'36	98	38.8	104	39.1	$1^{11}/_{12}$	117	40.4	$1^{5}/_{6}$	112	41.8	$1^{1}/_{3}$
	6	♂	2.10	24.X.	93	38.4	80	38.8	$1^{11}/_{12}$	119	41.0	2	92	41.7	$1^{1}/_{2}$
	7	♂	2.15	28.X.	107	37.6	114	39.1	$1^{1}/_{2}$	118	40.7	$1^{5}/_{12}$	111	41.2	$1^{11}/_{12}$
	8	♂	1.80	3.X.	115	37.7	108	38.3	$1^{5}/_{12}$	115	40.4	$^{5}/_{6}$	101	41.1	$2^{1}/_{3}$
	Mean		1.98		103	38.1	102	38.8	$1^{1}/_{3}$	117	40.6	$1^{1}/_{2}$	105	41.5	$1^{3}/_{4}$
Control experiment	5′	♂	1.76	11.X.	106	38.4	108	40.5	$1^{11}/_{12}$	142	41.3	$2^{1}/_{6}$	138	42.0	$1^{2}/_{3}$
	6′	♀	1.85	24.X.	93	38.6	115	39.1	$1^{11}/_{12}$	149	39.7	$2^{5}/_{6}$	131	42.5	$1^{5}/_{6}$
	7′	♀	1.75	28.X.	119	38.1	109	39.4	$1^{1}/_{2}$	151	41.0	$2^{1}/_{4}$	132	41.3	$1^{2}/_{3}$
	8′	♀	1.80	3.XII.	105	38.5	100	40.1	$1^{5}/_{12}$	154	42.3	$1^{2}/_{3}$	142	42.5	$1^{1}/_{6}$
	Mean		1.79		106	38.4	108	39.5	$1^{2}/_{3}$	149	41.1	$2^{1}/_{4}$	138	42.1	$1^{2}/_{3}$

this was on the whole 0.16%.

In passing it may be added: In some rabbits (11, 12, 17, 17′, 18, 18′ & 19, 19′) cane sugar was given in addition to the routine feeding in a dose of 10 g. for three or five (19′) days. Only Rabbit 19′ gave an extraordinary degree of hyperglycemia as 0.23%, which was estimated at the end of experiment, that is, five hours after starting to heat.

SUMMARY

Two sets of rabbits, normal individuals as the control and those long surviving depriviation of the splanchnici or the adrenals, were heated by means of combination of the heat-puncture and the heating in a special heating chamber. The head of rabbits was kept out of chamber, so that the animal breathe in the common air, not of abnormally high temperature.

1. When the environmental temperature was adjusted at 50°, the hyperthermia and hyperglycemia, such as mean 42°–43°C. and 0.15-

II

Adrenalectomized Rabbits and the Normal Rabbits on Environmental Temperature

At highest environmental temp.			Blood sugar when body temperature at 40°C.	Heart rate per min.	Frequency of respiration per min.	Special heating °C.	Room temperature °C.	Adrenalectomy					
								R			L		
Blood sugar mg%	Body temp. °C.	Hours from heating h.						Date	Body weight kg.	Gland weight mg.	Date	Body weight kg.	Gland weight mg.
112	41.8	1 1/3	102	240–324	54–156	44–50	19–22	23.III.	1.28	80	19.V.	1.40	90
95	41.7	1 1/2	106	252–336	48–216	45–55	9–12	7.V.	1.55	90	25.V.	1.55	95
118	40.7	1 5/12	99	240–288	60–210	50–55	12–14	2.V.	1.35	70	28.V.	1.65	85
115	40.4	5/6	80	300–384	60–168	48–58	11–20	9.V.	1.35	70	1.VII.	1.40	140
110	41.2	1 1/3	97	258–333	56–188	47–53	13–17		1.38	78		1.48	102
126	41.3	1 1/6	118	240–324	54–144	45–50	19–22						
123	42.2	1 2/3	120	240–318	60–246	45–55	9–12						
114	41.0	1 1/4	114	270–360	54–120	50–55	12–14						
108	41.5	2/3	106	240–348	72–258	48–53	11–20						
118	41.5	1 1/6	112	248–338	60–192	47–53	13–17						

0.17%, were brought about in the control animals, and those of 41°–41.5°C. and 0.11–0.12% in the animals, suffered from splanchnicotomy or adrenalectomy.

2. The chamber temperature be raised to 60,° the hyperthermia and hyperglycemia were estimated as 43°–44°C. and 0.14–0.17% in the control animals, and 42.5°–43°C. and 0.14% in the individuals operated on.

Otherwise expressed:

(A) While the heat-puncture alone cannot produce such a high temperature as 42° or more, and induce a blood sugar increase, except the so-called operation hyperglycemia, it effects a considerable hyperthermia and hyperglycemia as well, if artificial heating of animal body be combined to it. 50° and 60° of the environmental temperature act so.

(B) Splanchnicotomy and adrenalectomy effect to reduce the hyperthermia and hyperglycemia, thus occurring. These effects are con-

TABLE

Blood Sugar Content and Body Temperature of Doubly and 60° Environ-

	No. of experiment	Sex	Body weight	Date of experiment	Initial		Before special heating			Maximal blood sugar			At highest body temperature		
					Blood sugar mg%	Body temp. °C.	Blood sugar mg%	Body temp. °C.	Hours after puncture	Blood sugar mg%	Body temp. °C.	Hours from heating	Blood sugar mg%	Body temp. °C.	Hours from heating
Principal experiment	9	♂	2.00	27.XI.'36	96	37.8	96	38.4	$1^{11}/_{12}$	132	42.9	$1^{1}/_{6}$	132	42.9	$1^{1}/_{6}$
	10	♂	1.90	10.XII.	106	38.4	101	38.9	$1^{11}/_{12}$	149	41.0	$2^{1}/_{3}$	129	42.5	$1^{1}/_{3}$
	11§	♀	1.90	11.I.'37	92	38.0	96	38.6	$1^{11}/_{12}$	123	43.0	$1^{1}/_{3}$	123	43.0	$1^{1}/_{3}$
	12§	♂	1.85	13.I.	99	38.5	97	39.6	$1^{5}/_{12}$	127	42.6	$^{5}/_{6}$	119	43.0	$1^{1}/_{3}$
	13*	♂	2.20	27.I.	104	38.6	110	39.2	$1^{1}/_{2}$	157	42.5	2	123	43.6	$1^{1}/_{2}$
	14*	♂	2.20	30.I.	90	38.5	91	39.1	$1^{1}/_{2}$	136	40.4	$2^{1}/_{2}$	120	42.4	$1^{1}/_{2}$
	Mean		2.01		98	38.3	100	38.9	$1^{2}/_{3}$	137	42.1	$1^{2}/_{3}$	124	42.9	$1^{1}/_{3}$
Control experiment	9′	♂	1.50	27.XI.'36	96	37.5	104	39.1	$1^{11}/_{12}$	148	43.8	$1^{5}/_{6}$	108	44.4	$1^{1}/_{3}$
	10′	♀	1.80	10.XII.	96	38.4	111	39.6	$1^{11}/_{12}$	158	41.8	$2^{1}/_{2}$	126	43.2	$1_{1}/_{2}$
	11′	♂	1.85	11.I.'37	91	38.2	96	40.5	2	147	42.5	1	139	43.2	$1^{1}/_{2}$
	12′	♀	1.85	13.I.	111	38.8	103	40.8	$1^{1}/_{2}$	163	42.8	2	159	44.2	$1^{1}/_{2}$
	Mean		1.75		99	38.5	104	40.0	$1^{11}/_{12}$	154	42.8	$1^{5}/_{6}$	133	43.8	$1^{5}/_{12}$

* No control experiment. § Fed with cane sugar.

spicuous when 50°-heating is applied whereby both the variations are of lesser degree. Especially the effect upon the hyperglycemia is distinct. But the splanchnicotomy and adrenalectomy can not reduce so strongly the hyperglycemia and hyperthermia, when the environmental temperature be arranged high as 60°.

References and Notes

1) Itikawa, Tohoku J. Exp. Med., 1935, **27**, 473.

* This tendency was noted in Furonaka, Chosen Igakukai Z., 1930, **20**, 189.

III

Splanchnicotomized Rabbits and the Normal on Heatpuncture mental Temperature

At highest environmental temp.			Blood sugar when body temperature at 40°C.	Heart rate per min.	Frequency of respiration per min.	Special heating °C.	Room temp. °C.	Splanchnicotomy	
Blood sugar mg%	Body temp. °C.	Hours from heating						Date	Body weight
124	41.9	2/3	103	288–390	60–174	45–59	14–20	12.IX.'36	1.80
129	42.5	1 1/3	104	288–366	60–180	50–60	11–15	8.X.	1.45
123	43.0	1 1/3	109	288–372	60–126	57–58	6–13	22.X.	1.85
127	42.6	5/6	108	282–360	60–180	54–58	8–14	22.X.	1.30
123	43.6	1 1/2	107	300–414	60–126	50–60	8–12	24.IX.	2.00
134	41.8	1	113	300–366	60–156	50–60	10–13	8.X.	1.50
127	42.4	1 1/6	107	291–378	60–157	51–59	10–16		1.50
106	42.8	5/6	103	264–408	60–204	54–59	14–20		
126	43.2	1 1/2	101	288–372	60–192	50–60	11–15		
147	42.5	1	110	288–330	66–192	45–58	6–13		
143	42.8	1	103	288–390	72–168	54–58	8–12		
131	42.8	1 1/12	107	282–375	65–189	49–59	10–15		

TABLE

Blood Sugar Content and Body Temperature of
on Heat-puncture and 60°

	No. of experiment	Sex	Body weight	Date of experiment	Initial		Before special heating			Maximal blood sugar			At highest body temperature		
					Blood sugar mg%	Body temp. °C.	Blood sugar mg%	Body temp. °C.	Hours after puncture	Blood sugar mg%	Blood temp. °C.	Hours from heating	Blood sugar mg%	Body temp. °C.	Hours from heating
Principal experiment	15	♂	2.10	30.X.'36	107	37.7	111	38.5	1⁵/₁₂	143	40.5	2⁵/₆	116	42.5	1¹/₃
	16*	♀	1.95	5.XII.	101	38.4	109	39.3	1¹/₂	139	42.7	1¹¹/₁₂	134	42.9	1⁵/₁₂
	17§	♂	2.15	15.XII.	115	38.3	103	39.5	1²/₃	132	42.5	1⁵/₁₂	132	42.5	1⁵/₁₂
	18§	♂	2.10	24.XII.	83	38.6	81	39.9	1⁵/₆	125	42.7	1⁵/₁₂	125	42.7	1⁵/₁₂
	19§	♂	2.20	20.I.'37	90	38.4	93	38.6	1⁵/₁₂	139	41.0	2¹/₂	106	42.3	1¹/₂
	20*	♀	2.15	25.I.	98	38.4	108	38.8	1¹/₂	143	42.0	1⁵/₆	126	42.8	1¹/₃
	Mean		2.11		99	38.3	101	39.1	1¹/₂	138	41.8	2	123	42.6	1⁵/₁₂
Control experiment	15′	♂	1.60	30.X.'36	104	38.2	109	38.9	1⁵/₁₂	161	42.0	2²/₃	135	43.2	1¹/₆
	17′§	♂	1.50	15.XII.	96	38.9	112	40.1	1²/₃	144	41.2	2¹/₄	132	42.6	1¹/₄
	18′§	♀	1.65	24.XII.	83	38.9	84	39.8	1⁵/₆	151	41.5	2¹/₄	117	42.9	1³/₄
	19′§	♂	1.75	20.I.'37	99	38.5	94	39.5	1⁵/₁₂	233	39.2	4⁵/₆	182	42.7	1⁵/₆
	Mean		1.63		96	38.6	100	39.5	1⁷/₁₂	172	40.8	3	142	42.9	1¹/₂

* No control experiment. § Fed with cane sugar.

IV

Doubly Adrenalectomized Rabbits and the Normal Environmental Temperature

At highest environmental temp.			Blood sugar when body temperature 40°C. mg%	Heart rate per min.	Frequency of respiration per min.	Special heating °C.	Room temperature °C.	Adrenalectomy					
								R			L		
Blood sugar mg%	Body temp. °C.	Hours from heating						Date	Body weight kg.	Gland weight mg.	Date	Body weight kg.	Gland weight mg.
116	42.5	1 1/3	116	364–312	66–180	45–60	13–15	7.V.'36	1.50	100	23.VI.'36	1.80	330
139	42.9	1 11/12	106	240–360	72–306	53–59	11–16	7.V.	1.56	90	9.VI.	1.65	142
123	41.3	11/12	99	214–372	108–180	54–55	11–18	14.VII.	1.70	63	10.IX.	2.00	217
125	42.7	1 5/12	101	300–417	66–234	50–56	11–15	6.VII.	1.44	84	3.IX.	1.60	103
106	42.3	1 1/2	101	364–384	66–192	43–58	10–16	25.VI.	1.40	70	20.VII.	1.40	103
126	42.8	1 1/3	111	270–360	66–180	45–60	10–16	9.VII.	1.50	83	6.X.	1.95	158
123	42.4	1 5/12	106	285–369	74–212	48–58	11–16		1.54	82		1.73	176
109	42.9	2/3	102	270–372	66–138	45–60	13–15						
129	41.9	3/4	89	240–360	54–192	54–55	11–18						
117	42.9	1 3/4	106	300–360	66–312	50–56	11–15						
158	42.4	1 1/3	102	240–372	60–180	43–58	10–16						
128	42.5	1 1/6	100	260–366	62–206	48–57	11–16						

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Isolation of a Virus from a Sporadic Case of Izumi Fever

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"Izumi Fever" is one of the important exanthematic diseases in this country, which is confined almost to children and may occur either in a sporadic or in an endemic form. It is characterized by a transient fine rash resembling that of scarlatina and followed by some intestinal disorders.

Many authors have endeavoured to isolate the virus and to establish their causative nature, but almost all of them failed in volunteer experiments. We succeeded to produce a typical infection in an 8-years-old female by an oral administration of the isolated virus. After 4 days incubation period, saddle-back type fever, bilateral exanthema of arms, angina and urobilinogen in urine were recognized and the study is now in progress to isolate the same virus from feces and blood of this child again.

The virus was isolated from a sporadic case by intracerebral inoculation of the Berkefeld filtrate of feces to young mice. Subsequently the virus was transferred from brain to brain and now fully adapted to mice. These mice usually dies until 5 days after inoculation and LD_{50} for mice weighing 8 g. in average is $10^{-8.5}$. They are stored in 50% glycerol for a month without loss of activity. Histopathological changes in mice were more conspicuous at the begining of isolation of the virus in liver, spleen and kidney, but later chiefly focused in brain, causing encephalitis and leptomeningitis. Egg culture and purification of virus were performed, but succeeded not yet.

Neutralization antibody against this virus was proved in the serum of patient from whom the virus was isolated 3 and 4 month after onset. Complement fixation test was also performed.

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Genetical Studies on Skin Diseases

IX. Multiple Follicularcyste (Bosselini)

By

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" Multiple Follicularcyste " in Japan was reported first by Komaya[1] (1922), and then the detailed reports by Hashimoto,[2] Mukai,[3] Minami[4] and other authors followed. Siemens,[5] Itô,[6] Mukai and Noojin-Reynolds[7] called attention to the inheritance of this disorder, but the lack of sufficient details of the family history makes this problem remain still unsolved.

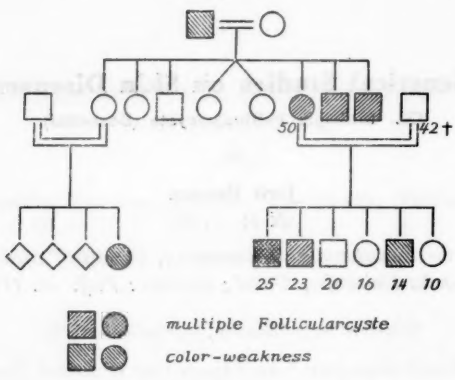
I examined a case of this disease and studied statistically from genetical point the cases collected from Japanese literature.

Case Report

Mr. N. F. aged 25 came to our clinic in Aug. 1951. Healthy appearance and no visible anomaly of development excepting color-weakness. His father died of lymphosarcoma, and 6 members in his family had the same skin disease (Fig. 1). Color-weakness was seen in both one of his brothers and his cousin. He could not notice the biginning of his disorder. Since he had noticed the presence of these nodules, they became gradually enlarged and remained in various sizes. The nodules were distributed on the front, hair-covered head surface, neck, back, groin, thighs and arms. No nodules on the scrotum, ears and periauricular regions. The number of these nodules was 500 and more in total. They adhered to the overlying skin but not to the subcutis. They were uncolored, except a few ones with a slight-bluish tone, tumorlike nodules varying in size from pin-head to sparrow-egg. The nodules on the arms and thighs were so small that they could be noticed only by palpation, but they were larger in size on the neck, back, chest and groin. Most of them were palpable in elastic firm, but on larger nodules was pseudo-fluctuation noticed and cream- or butterlike fluid escaped along the needle by puncture.

Cholesterol in blood was 272 mg/dl, other blood examinations pre-

Fig. 1



sented no abnormal results.

Histological Findings; Epidermis normal. Large cyst which contains sudanophilic homogene substance is distributed from cuits to subcutis. The wall of cyst consists of 1–3 layers of epithelial cells and connective tissue. On the innermost of cyst wall is seen keratin lamellae. Atrophic sebaceous gland cells are found in corporation to a part of the cyst wall. Follicle mouth is usually dilated and keratotic plug seen there. There are cellular infiltrations around cyst wall which consist of epitheloid cells, round cells and giantcell-like cells. Outside of these cells, perivascular round cell infiltration is slightly found. The figure of lipophagy in fatty tissue also can be found.

Comment

This disorder was variously named by different authors from their points of view: multiple Follicularcyste (Bosselini,[8] 1898), steatocystoma multiplex (Pringle,[9] 1899), Sebocystomatosis (Günther,[10] 1917), multiple sebaceous cysts (McPhedrom,[11] 1905), maladie polikystique épidermique héréditaires (Sézary et Levy-Coblenz,[12] 1931), Nevo-cystico-tricoseboceo diffuso (Lisi, F.,[13] 1932), etc.

Thirty-three cases including the present case were collected from Japanese literature and studied statistically from the genetical view point. Sex: 4 females and 28 males. This shows that this disease is seen more frequently in males as Mount,[14] Lisi, etc. had observed. Most of the patients become first aware of their disease in their age of 15–25 years (Table I). The cases with no statement of family history are 11, and in 7 out of 22 cases with family history, is the family occurrence of this disorder given: in 1 case it occurred through 3 generations, in 5 cases

through 2 generations and in 1 case in two brothers.

About pathogenesis, Bossellini, Pringle, Komaya and many other authors gave a role to hyperkeratosis in follicle, and Schaumann[15] added to this the anatomic malformation of sebaceous gland mouth. Moreover, Noodjin-Reynolds suggested the role of transmitted lipoid metabilic abnormality.

TABLE I

Age years	Case
1—10	1
11—15	1
16—20	13
21—25	8
26—30	4
30—	2
?	4

In my case as in Noodjin-Reynolds' case, cholesterol in blood showed abnormally high contents. It shows that the patients had lipoid metabolic abnormality. From this it is suggested that this disorder is connected with lipoid metabolic abnormality. The fact that lipoid metabolism is most active in puberty, when the appearance of this disease is most frequently observed, is favorable to this assumption. It seems to be logical to assume that the cyst formation is due to the transmitted malformation of sebaceous gland mouth, accelerated by both lipoid metabolic abnormality and hyperkeratosis. It is very natural that the hyperkeratosis and malformations of the sebaceous gland mouth are found in various degrees. Therefore the lesions can present different appearances varying from apparent nodules to the ones which are so slightly affected that it is impossible to diagnose them as this disease. In family history, the latter ones cannot be recognized as this disease. From the above, it is considered that this disease is inherited in dominant type containing so-called latent case in the abovementioned sense, though Siemens describes that it presents "indefinite" dominante type and Noodjin-Reynolds writes "responsible single" dominant.

In histological findings, cell infiltration around cyst-wall was usually reported, and Schaumann, Lisi, Yamazaki[16] and Mukai found giant cells. Yamazaki reported remarked cell infiltration around atrophic hair-root attended to the cyst. Comparatively remarkable cell infiltration was seen also in my case. But similar histological finding with giant cells is seen in epithelioma adenoides cysticum, which is the disease with similar cyst based on the congenital disposition (Itô,[17] Yamazaki,[18] Maschkilljsson,[19] etc.). Therefore, this finding seems to be based on the effect of the cyst and not to work as etiological factor.

No complication was reported in 7 cases out of 10, and in 23 cases is given no statement of complication. Only 3 cases presented some complications: lipoma and nevus molis (Yamazaki), nail anomaly (Taniguchi-Sozu[20]) and color-weakness by the present author.

Conclusion

A case of "multiple Follicularcyste" was reported. Six patients were found to have had this disease through 3 generations. A genetical study of the 33 cases collected from Japanese literature was made, and the author concluded that this disease is inherited in dominant type.

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Studies on Reticulo-Endothelial System

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It seems rather difficult that only one method can successfully be employed to tell completely the intricate function of the reticulo-endothelial system. Adler-Reimann[1] initiated the congo-red test in 1925 and measured the congo-red indices, asserting that lower values would indicate the accelerated function and higher values the dull function of the system. Our investigations[2] revealed that the congo-red indices would show satisfactorily the functional activity of the reticulo-endothelial system. Therefore, I made an attempt to measure the congo-red indices given by various diseases and make clear the clinical significance of the test.

Experimental

Method

The congo-red indices in healthy persons lie, according to Adler-Reimann[1], between 50–70%, but Akashi and others[3] count 51.3–72.2% as the normal range, Ueda and others[4] 47–80%. I measured those of 8 healthy adults by Adler-Reimann's original method and found the lowest and the highest values to be 51.1% and 72.0% respectively. In this study, therefore, 50–72% were regarded as the normal range for congo-red indices.

Results

1) Liver diseases

Congo-red indices from 93.9 to 57.8 (average 80.8) were obtained in 24 patients who had been diagnosed as certain cases of liver diseases by clinical observation, needle-biopsy, operation, and autopsy in our medical Clinic. 18 of them presented high values (75%).

4 cases of carcinoma of the liver and the bile duct exhibited the high values 85.7–93.3, all accompanied with intensive jaundice. Of 4 cirrhosis cases, 3 were accompanied with jaundice and showed high values. The

other one case without jaundice, which was accompanied with considerable ascites and an enlarged liver and spleen as well as clinical features of cirrhosis—at last died— showed a remarkable derangement of the liver function, but the congo-red index was 69.8, normal. As to hepatitis or icterus catarrhalis, 2 acute severe cases showed such high values as 92.0 and 90.6 for their congo-red indices. One of the two cases decreased later to 83.9 in the index, coincident with improvement of an enlarged liver and jaundice. The other one, slightly jaundiced and not so marked in clinical features as the first two cases, showed 80.6, and a still milder one a little higher value than the normal. With cholelithiasis and cholecystopathy, 5 patients with the former disease were all jaundiced, of whom 3 had 86.0, 85.5 and 84.6 as their congo-red indices. Two others, who afterwards were cured of the disease by internal treatment, had 75.9 and 68.7. This value 75.9 was lowered to 70.7, the normal value, as he was perfectly recovered. Three cases of cholecystopathy, without jaundice, showed all normal values. A slightly high value 75.6 of a patient with abscess of the liver decreased to 65.5, on disappearance of his clinical symptoms. Of 2 cases of clonorchiasis, one showed 89.9, the other the normal value (Table I).

Next considering the relation of the presence of jaundice with the value of congo-red index, it is shown in Table II. Among 24 liver patients, 16 out of 17 cases with jaundice, showed high values, though only 2 out of 7 cases without jaundice showed high values. This difference is statistically significant.

Further, in what relation does the congo-red index stand to the intensity of jaundice determined by the bilirubin index? The results of the examination are given in Table III: 6 cases which revealed high values of over 90 of congo-red index, were always accompanied with intensive jaundice, and 6 out of 7 cases which showed the smaller values of over 80, revealed a moderate intensity of jaundice, and at last 4 out of 5 cases which showed relative low values of over 73, were accompanied with slight jaundice.

This led me to think there might be some close relation between the intensity of jaundice and congo-red index. Calculation of correlation coefficient between congo-red indices and bilirubin indices gives, as shown in the lower space of Table III, $r=+0.613$. This is highly significant.

2) Gastric cancer, gastric and duodenal ulcers

a) *Gastric cancer:* As to 19 cases of gastric cancer congo-red indices were found to be from 48.3 to 89.5 (average 72.2), of which 11 were found with high values (58%).

There were some who showed high values 81.1 and 78.1 and in

TABLE I

Name	Sex	Age	Diseases of liver	Congo-red index	Bilirubin index	Takata reaction	Urobilinogen in urine	Prognosis
N.T.	♂	62	Carcinoma of liver with carcinomatous peritonitis	92.6	30	##	##	Dead
Y.N.	♂	42	Carcinoma of bile duct with liver metastasis	91.3	180	+	+	Progress.
Y.K.	♂	69	Carcinoma of bile duct	90.0	156	+	+	Dead
K.K.	♂	47	"	85.7	150	##	−	Dead
I.M.	♀	32	Cirrhosis of liver	93.9	250	##	−	After oper. died
S.H.	♀	41	"	86.2	125	##	±	Oper.
S.T.	♂	31	"	79.9	34	##	##	Better
S.A.	♂	26	"	69.8	no jaundice	++	##	Dead
M.S.	♂	41	Acute hepatitis	92.0	140	##	+	Better
H.T.	♂	24	"	90.6	85	##	−	Cured
S.S.	♀	23	"	80.6	30	+	−	"
S.M.	♂	26	Icterus catarrhalis	79.0	100	+	+	"
S.K.	♂	49	"	73.9	15	+	±	"
T.S.	♀	58	Cholelithiasis	86.0	95	+	++	Oper.
K.O.	♂	57	"	85.5	22	±	+	"
U.T.	♀	63	"	84.6	54	+	−	"
S.I.	♂	36	"	75.9	45	##	+	Cured
K.I.	♂	51	"	68.9	15	±	±	"
M.M.	♂	42	Clonorchiasis sinensis	89.9	no jaundice	+	−	Better
Y.T.	♂	65	"	71.4	"	+	−	"
T.F.	♀	47	Abscese of liver	75.6	"	−	##	Cured
K.M.	♂	51	Cholecystopathy	69.2	"	−	−	Better
K.A.	♂	20	"	68.5	"	−	−	Cured
C.S.	♂	36	"	57.8	"	−	−	"

TABLE II

Jaundice \ Congo-red index	High value	Normal value	Total
Liver disease with jaundice	16	1	17
Liver disease without jaundice	2	5	7
Total	18	6	24

$\alpha = 0.0027$ Level of significance below 1%.

these cases metastasis to the liver was clinically obvious. Some others showed 89.5, 84.8 and 83.3, and in these cases metastasis and adhe-

TABLE III

Diseases of liver	Congo-red index (X)	Bilirubin index (Y)
Cirrhosis of liver	93.9	250
Carcinoma of liver with carcinomatous peritonitis	92.6	30
Acute hepatitis	92.0	140
Carcinoma of bile duct	91.3	180
"	90.0	156
Acute hepatitis	90.6	45
Cirrhosis of liver	86.2	125
Cholelithiasis	86.0	95
Carcinoma of bile duct	85.7	150
Cholelithiasis	85.5	22
"	84.6	54
Acute hepatitis	80.6	30
Icterus simplex	79.0	100
Cirrhosis of liver	78.9	34
Cholelithiasis	75.9	45
Icterus simplex	73.9	15
Cholelithiasis	68.9	15

$\Sigma X = 1435.6$. $\Sigma Y = 1486$. $\Sigma(X-\overline{X})^2 = 837.6$. $\Sigma(Y-\overline{Y})^2 = 76949$.

$\Sigma(X-\overline{X})\,(Y-\overline{Y}) = 4922.4$. $r = \dfrac{\Sigma(X-\overline{X})\,(Y-\overline{Y})}{\sqrt{\Sigma(X-X)^2\Sigma(Y-Y)^2}} = +0.613$.

sions were only in a slight degree, so that gastrectomy was easily performed. There were yet others who showed 77.8, 72.5 and 71.4, and in these cases gastrectomy was seldom performed because of the difficulty caused by severe adhesions and metastasis. So far as gastric cancer, there seems to be no certain rule to follow. However, those in whom carcinomatous peritonitis was discovered before or after operation, had normal or lower values of congo-red index in most cases (Table IV). Table V is a tabular comparison of congo-red indices in 17 cases of gastric cancer, except metastasis to the liver, after having divided them in two groups—the possibility and the impossibility of gastrectomy. Among 8 belonging to the former group 6 showed above 73, 2 remaining within the normal limits. In the latter group 3 showed more than 73, while 6 gave the normal or lower value. It is to be noted that the last 6 were all accompanied with carcinomatous peritonitis.

b) *Gastric and duodenal ulcers:* 8 cases out of 19 gastric and duodenal ulcer cases showed high values of congo-red index (42%), though all fell between 55.3 and 93.5, average being 71.1. In the cases of gastric

TABLE IV

Name	Sex	Age	Diagnosis	Congored-index	Ascites	Operation
T.T.	♂	52	Castric cancer	89.5	—	Subtotal gastrectomy
H.E.	♀	39	"	84.8	—	"
Y.K.	♂	52	Gastric cancer with myodegeneratio cordis	83.3	—	"
R.T.	♀	53	Cancer of cardia	77.8	—	Total gastrectomy
T.C.	♀	52	Gastric cancer	72.5	—	"
A.N.	♀	48	"	71.4	—	Subtotal gastrectomy
K.K.	♂	61	Cancer of cardia	84.2	—	Possible, not operated
K.T.	♀	45	Gastric cancer	66.6	—	"
S.T.	♀	58	Gastric cancer with liver metastasis	81.1	##	Impossible, dead
G.W.	♂	53	"	78.1	—	Laparotomy
N.S.	♂	21	Gastric cancer	75.8	+	"
F.S.	♂	38	"	75.4	—	Impossible, not operated
S.S.	♂	65	"	82.0	+	Laparotomy
G.S.	♂	52	Gastric cancer with carcinomatous peritonitis	67.5	++	"
K.S.	♂	42	"	64.9	++	"
J.T.	♂	46	"	62.2	##	Subtotal gastrectomy
K.N.	♂	45	"	55.1	##	Impossible, not operated
I.T.	♂	31	"	53.0	+	Laparotomy
H.T.	♀	32	"	48.3	##	"

TABLE V

Gastrectomy \ Congo-red index	High value	Normal or low value
Possible	6	3
Impossible	3	6

ulcer, 4 with big niche showed high values, 93.5, 85.7, 83.3 and 77.2, 2 cases with lesser niche 75.6 and 75.4, a little higher than the normal, and the other two, in which the niche was as big as the tip of the little finger, 68.2 and 68.1, normal. Gastric ulcers seemed to show a tendency to increase their congo-red indices as the niche grew bigger. On the other hand, in all of the three cases of bleeding gastric

TABLE VI

Name	Sex	Age	Diagnosis	Congo-red index	Prognosis
G.T.	♂	56	Gastric ulcer (big niche)	93.5	Cured
Y.Y.	♀	57	"	85.7	"
T.S.	♂	55	"	83.3	Operated
S.T.	♂	44	"	77.2	Better
B.K.	♂	55	Gastric ulcer	75.6	Cured
H.S.	♀	51	"	75.4	"
S.S.	♂	48	"	68.2	Better
K.S.	♂	51	"	68.1	"
M.S.	♂	52	Bleeding gastric ulcer	64.1	"
S.M.	♂	53	"	59.5	"
T.H.	♂	43	"	53.0	Cured
M.O.	♀	69	Duodenal ulcer with pyloric stenosis	83.3	Operated
H.T.	♂	43	"	74.9	"
Y.S.	♂	38	Dudenal ulcer	71.2	Better
K.T.	♂	44	"	68.4	"
T.K.	♂	48	"	68.0	"
K.M.	♂	36	"	64.1	Operated
T.Y.	♂	35	"	62.4	Better
M.K.	♂	39	"	55.3	"

ulcer, though large ulcers were observed, normal values 64.1, 59.5 and 53.0 were exhibited.

In the cases of duodenal ulcer, all showed normal values, except 2 with pyloric stenosis which showed higher values 83.3 and 74.9 (Table VI).

3) Tuberculous diseases and other diseases

a) *Tuberculous diseases:* 6 out of 10 tuberculosis patients showed high values. In the case of acute tuberculosis the values were comparatively high, being 86.2, 82.5 and 77.1. The value of one patient whose fever had been high and whose sputum had been large in quantity was reduced to the normal 63.8 in 14 days after streptomycin was tried, which served to prevent a worse condition.

In the cases of tuberculous diseases in which the prognosis is bad, the congo-red index shows a high value. But when it becomes better, the value tends to lower to the normal range. However, tuberculous peritonitis with exudation has a lower value than normal. Incidentally, two cases of pulmonary gangrene showed 77.0 and 75.8 for their values, both being a little higher than normal.

b) *Diseases with splenic tumour:* As to 5 patients with splenic tumour,

TABLE VII

Name	Sex	Age	Diagnosis	Congo-red index
C.I.	♂	31	Pulmonary tuberculosis	86.2
K.K.	♂	20	"	82.5
S.S.	♀	40	"	77.1
C.M.	♀	24	"	79.1
K.T.	♂	32	"	73.5
Y.S.	♂	22	"	72.0
T.H.	♀	47	" with renal tuberculosis	63.4
T.O.	♀	29	Pleuritis exudativa dextra	77.7
K.S.	♀	53	Peritonitis tuberculosa	67.5
B.H.	♂	55	"	45.7
C.E.	♂	43	Pulmonary gangrene	77.0
K.Y.	♂	38	"	75.8
K.A.	♂	27	Kala azar	26.6
S.N.	♂	29	"	82.4
T.A.	♂	55	Retothelsarcoma	64.2
K.I.	♂	19	Leucemia	59.1
M.M.	♀	39	Banti's disease	56.1
A.N.	♀	33	Anemia	74.5
H.S.	♂	36	Chronic nephritis with anemia	70.1
T.S.	♀	45	Diabetes mellitus	76.2
U.S.	♂	20	"	59.1
F.F.	♀	41	Graves' disease	57.1
S.H.	♀	48	Toxic goiter	67.7
T.N.	♀	41	"	50.7
H.O.	♀	49	Acromegaly	61.2
T.T.	♂	43	Amoebic dysentery	93.7
T.G.	♂	22	"	64.8
N.I.	♂	35	"	67.9
K.N.	♂	43	Cardiac insufficiency	76.2
I.F.	♂	49	Chronic alcoholism	68.9

that is, 2 cases of kala-azar, one case each of Banti's disease, leucemia and retothelsarcoma, their values of congo-red index were measured. Of the 2 kala-azar patients, one, in whom enlargment of the liver and the spleen were very obvious, gave a much lower value 26.6, but after three months' medical care the swelling went down and the general findings were good, when the value was almost normalized to 48.2. The case in which an enlargement of the liver and the spleen was not so obvious showed high value 82.4.

c) *Diseases of the endocrine organs:* Examinations made of 2 patients

of diabetes mellitus, 3 of thyroid diseases and one of acromegaly revealed only one case of diabetes mellitus in which the value was higher than normal. All others exhibited normal values.

d) *Other diseases:* This test was tried on other diseases: amoebic dysentery, essential hypochromic anemia, anemia with chronic nephritis, heart insufficiency and chronic alcoholism. One amoebic dysentery having severe diarrhea, essential hypochromic anemia and heart failure with decompensation showed higher values than normal (Table VII).

Discussion

Liver diseases: In these experimental results high congo-red indices were found in 18 out of 24 cases of liver diseases (75%). Generally speaking, severe cases with carcinoma of the liver, carcinoma of the bile duct, cirrhosis or acute hepatitis showed high values. Out of 24, jaundice was observed in 17 cases, of which 16 revealed high values. In 7 others not accompanied with jaundice, only two cases showed high values. Therefore, it may be noted that in liver diseases high congo-red indices are, in most cases, found among those with jaundice. Next, 6 cases out of 24 were above 90 for the congo-red index and all of the six had average or higher intensity of jaundice determined by the bilirubin index. This showed that there is a correlation between the congo-red index and bilirubin

Table VIII

Name	Sex	Age	Congo-red index	Azorubin test (dye excreted by urine)		Bilirubin index
				%	Time	
T.N.	♂	62	92.6	31.68	17	30
M.S.	♂	41	92.0	51.05	23	140
Y.N.	♂	42	91.3	49.86	17	180
H.S.	♀	41	86.2	55.11	11	125
T.S.	♀	58	86.0	58.57	24	95
K.K.	♂	47	85.7	52.88	24	150
K.O.	♂	57	85.5	24.04	9	22
S.I.	♂	36	75.9	28.74	11	45
S.K.	♂	49	73.9	48.29	23	15
K.T.	♂	65	71.4	11.05	5	No jaundice
S.A.	♂	26	69.8	31.09	9	"
K.M.	♂	51	69.2	16.44	4	"
K.I.	♂	51	68.7	16.17	5	15
A.K.	♂	20	68.5	24.29	5	No jaundice
C.S.	♂	36	57.8	15.04	4	"

TABLE IX

Disturbance \ Method	Congo-red index	Azorubin test	Total
Positive	9	14	23
Negative	6	1	7
Total	15	15	30

$\alpha = 0.038$ Level of significance below 5%.

TABLE X

Azorubin test \ Jaundice	With jaundice	Without jaundice	Total
Distrubed	10	4	14
Not distrubed	0	1	1
Total	10	5	15

$\alpha = 0.33$

TABLE XI

Congo-red index \ Jaundice	With jaundice	Without jaundice	Total
Disturbed	9	0	9
Not disturbed	1	5	6
Total	10	5	15

$\alpha = 0.002$ Level of significance below 1%.

index. In other words, the congo-red index increased in proportion to the bilirubin index.

Tables VIII and IX are a comparison between the results of the congo-red test and those of the azorubin S test which was carried out for the same 15 of 24 liver disease cases by T. Nakazima[6] of our Clinic. The observation from Nakazima's test showed a positive reaction in 14 cases and this writer in 9 cases. This difference is significant. Further comparison was made as to the presence of jaundice (Tables X, XI) and significant difference was noted in the case tested by congo-red dye, but not in that by the azorubin S test. In other words, in the azorubin S test almost all cases of liver diseases, irrespective of presence of jaundice, displayed abnormal, while in the congo-red test abnormality was more often observed in the cases with jaundice. This results suggest a close relation of the disturbance of the reticulo-endothelial system with the appearance

of jaundice.

Gastric cancer, peptic ulcer: Ueda and others[4] have reported that among 17 cases with cancer of the digestive organs 7 caused the reticulo-endothelial system to decrease in function (41%); the congo-red indices did not differ with the size of tumours, the values being likely to be higher with metastasis in the liver or poor nutrition. They observed that in 3 cases of 4 gastric ulcer patients the function of the reticulo-endothelial system decreased. The report of Adler-Reimann[1] gave 4 cases of the same disease with normal values. The results brought out by these experiments were that 11 of 19 gastric cancer cases showed high congo-red indices (58%) and those in which metastasis to the liver was observed showed, as Ueda[4] reported, comparatively high indices. Especially when metastasis and adhesions were very slight and gastrectomy was not difficult the values were high; when metastasis and adhesions were intense the values were not so high. Further, in cases of carcinomatous peritonitis the values were normal or lower. One can not make a hasty conclusion from these experimental results. In the case of gastric cancer we can not accurately determine the function of the reticulo-endothelial system by the congo-red test.

The congo-red indices of peptic ulcer patients were high when the niche was big and lower when it was small. Does not this fact suggest that the function of the reticulo-endothelial system has something to do with the causative factors of gastric ulcers? However, it is worth noting that in all the cases of bleeding gastric ulcer normal values for the congo-red index were found, though considerably large ulcers were observed. In duodenal ulcer cases only those with pyloric stenosis showed high congo-red indices.

Tuberculous and other dieases: Ueda's report[4] is that in tuberculosis of the lungs the function of the reticulo-endothelial system was not much disturbed in the sclerotic stage, while the disturbance of the system was great in exudative stage though the lesion was not so remarkable. Okada[5] says that the congo-red index is high according to the seriousness of the disease, and the value grows higher as the condition becomes worse. In those experiments 6 out of 10 tuberculosis patients showed high values. Exudative tuberculosis cases showed high values, sclerotic tuberculosis normal values, though extending in a wide range. It is observed that in tuberculous diseases when the prognosis is bad a high congo-red index is found, but the value shows the tendency to return to the normal range, coincident with improvement of the clinical manifestations.

Next, for the diseases of the spleen, which is next to the liver in importance. It is to be noted that of the two cases of kala-azar, one in

whom enlargement of the liver and the spleen was extremely marked, showed a remarkably small value, but when the swelling was decreased by medical treatment the value approached the normal range.

Congo-red indices of the patients with endocrinological diseases are, according to Ueda and others[4], high in many cases. But it was in only one case of diabetes mellitus out of 6 that the congo-red index remained high through our experiments. According to the classification of our Clinic, this was to be classified in Type II.

Among the cases of other diseases, one of 3 patients of amoebic dysentery, who was suffering from the severer diarrhea, showed a high congo-red index. A patient with hypochromic anemia and one of heart insufficiency with decompensation also showed high values.

Consequently, we may summarize the above observations in a few words high values of the congo-red index, generally speaking, indicate the seriousness of the diseases. However, it must be noted that in case of kala-azar the value, on the contrary, was extremely low.

Conclusion

By the congo-red method I examined the function of the reticulo-endothelial system in 92 patients—24 of liver diseases, 38 of gastric carcinoma and peptic ulcers, 30 of tuberculous and other diseases and had the following results:

1. The disturbance of the function of the reticulo-endothelial system was found in 75% of 24 liver patients and was more often found in cases with jaundice than without it.

2. There is some indication that the function of the system decreases in proportion to the intensity of jaundice.

3. The disturbance was found in 58% of 19 gastric cancer cases, in 55% of 11 gastric ulcer cases and in 25% of 8 duodenal ulcer cases.

4. Among the gastric cancer, 2 cases with metastasis to the liver displayed the disturbance, but none of the cases in which carcinomatous peritonitis coexisted had the function decreased.

5. In gastric ulcer cases the function of those having large ulcers tended to decline notably, but 3 cases of bleeding ulcer did not show the decline of the function. In duodenal ulcer patients, only two cases with pyloric stenosis displayed the decline of the function.

6. Out of 10 tuberculosis cases, 6 presented the disturbance. Generally speaking, this was observed when the condition of the disease was serious. The function returned to normal as the condition improved.

7. Among other diseases the decline in the function of the reticulo-endothelial system was found in one case of each of kala-azar, anemia, diabetes mellitus, amoebic dysentery and heart insufficiency. Other case

of kala-azar exhibited a value for lower than normal and it returned to normal on improvement of the condition.

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Studies on the Temperature of the Gastrointestinal Tract

Seventh Report

Response of the Intragastric Temperature to Histamine

By

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Response of the intragastric temperature of healthy men, especially young adults, to histamine was reported previously[1)2)] in comparison with other various drugs. In this report, a further study is presented selecting not only healthy men but also patients with several diseases of the digestive system, and men of various age groups.

Experimental

Methods and Materials

The intragastric temperature was measured simultaneously with the pulse rate, blood pressure and gastric juice after the same procedures as previously reported[1)]. 1:1000 solution of histamine hydrochloride was subcutaneously injected in a dose from 0.0093 to 0.0200 mg. per kg. to 100 individuals who are listed in Table I. The room temperature ranged between 11 and 24°C.

Results

The data of the changes in the intragastric temperature after the injection of histamine are given in Tables II and III, with the maximums, minimums and means of the injected dose, room temperature, age of the men tested and intragastric temperature before the injection. In Table II the changes in the case in which the materials are classified according to their diseases including healthy state and in Table III those classified according to their ages are illustrated, showing only the upper and lower limits and means of the changes at each time. Plotting the means in Tables II and III, respectively Figures 1 and 2 are obtained. The means of the changes in the pulse rate, diastolic blood pressure and

TABLE I

Age and Disease or State of 100 Individuals Tested

Age group	Sex	Number		Disease or state	Sex	Number	
15–20 years	♂ ♀	3 3	6	Healthy state	♂ ♀	18 8	26
20–29 years	♂ ♀	16 1	17	Gastric ulcer	♂ ♀	10 2	12
30–39 years	♂ ♀	9 7	16	Duodenal ulcer	♂ ♀	9 0	9
40–49 years	♂ ♀	20 5	25	Gastric cancer	♂ ♀	22 10	32
50–59 years	♂ ♀	20 10	30	Cholelithiasis	♂ ♀	8 6	14
60–70 years	♂ ♀	4 2	6	Gastrectomized state	♂ ♀	5 2	7
15–70 years	♂ ♀	72 28	100	Total	♂ ♀	72 28	100

gastric free acidity are illustrated in Figures 3 and 4.

DISCUSSION

At first the general views of the changes after the injection of histamine are given. Immediately following the injection, a flush of the face, heat sensation and palpitation were observed simultaneously with increases in the pulse rate and pulse pressure, and a drop in the diastolic blood pressure. The systolic blood pressure was also lowered, but the drop was smaller and variable by individuals. In succession to those changes, the intragastric temperature began to fall. The pulse rate reached the maximum increase of 16.4 per minute on an average, in the course of the first 10 minutes and thereafter it began to diminish recovering at 30 minutes after the injection (Fig. 3). About the same time the flush of the face and the palpitation gradually disappeared and cold sensation began to appear. The diastolic blood pressure reached the maximum drop of −22.2 mm. Hg at 10 minutes after the injection and recovered by 60 minutes (Fig. 3). In most cases the maximum drop of −0.20–−0.50°C of the intragastric temperature was observed at 15–20 minutes after the injection. The onset of the drop was somewhat later than those of the changes in the pulse rate and blood pressure. It recovered at about 60 minutes after the injection and its recovery was also later than those of the pulse rate and blood pressure (Fig. 1). The flush of the face, the heat sensation, the drop in the diastolic blood pressure and the increase

TABLE II

The Upper (U.L.) and Lower Limits (L.L.) and Means of the Changes in the Intragastric Temperature at Each Time after the Injection of Histamine, when the 100 Individuals Tested are Classified according to their Diseases Including the Healthy State

Disease or state		Age years	Room temp. °C	Dose mg./kg.	Before inject. °C	After injection (minutes)							
						5 °C	10 °C	15 °C	20 °C	30 °C	40 °C	50 °C	60 °C
Healthy state	U.L.	56	24	0.0200	38.1	–0.05	–0.10	–0.05	–0.05	0.05	0.05	0.25	0.25
	L.L.	16	12	0.0093	36.5	–0.50	–0.75	–0.75	–0.75	–0.70	–0.60	–0.45	–0.35
	Mean	31.7	16.0	0.0162	37.36	–0.21	–0.34	–0.42	–0.43	–0.34	–0.22	–0.12	–0.05
Gastric ulcer	U.L.	57	24	0.0178	37.5	0	0	–0.10	0	0.10	0.15	0.20	0.30
	L.L.	28	11	0.0096	36.5	–0.35	–0.50	–0.55	–0.50	–0.45	–0.25	–0.20	–0.15
	Mean	46.2	14.8	0.0144	37.02	–0.17	–0.25	–0.27	–0.23	–0.14	–0.06	–0.01	0.01
Duodenal ulcer	U.L.	48	16	0.0176	37.7	–0.10	–0.10	–0.10	–0.05	0.05	0.10	0.10	0.10
	L.L.	15	13	0.0100	36.8	–0.40	–0.45	–0.45	–0.45	–0.35	–0.15	–0.05	–0.05
	Mean	32.2	14.3	0.0159	37.41	–0.21	–0.29	–0.30	–0.24	–0.14	–0.06	0.02	0.05
Gastric cancer	U.L.	69	24	0.0178	38.2	0.05	0.05	0.05	0.05	0.15	0.15	0.20	0.25
	L.L.	32	12	0.0100	36.3	–0.30	–0.45	–0.45	–0.45	–0.35	–0.30	–0.30	–0.30
	Mean	49.1	15.6	0.0157	37.29	–0.10	–0.18	–0.21	–0.20	–0.15	–0.10	–0.05	–0.02
Cholelithiasis	U.L.	70	24	0.0175	38.0	–0.05	–0.10	–0.15	–0.05	–0.05	0	0.05	0.10
	L.L.	27	11	0.0100	36.9	–0.30	–0.45	–0.50	–0.55	–0.55	–0.45	–0.35	–0.20
	Mean	46.6	15.9	0.0162	37.44	–0.14	–0.24	–0.29	–0.29	–0.22	–0.13	–0.07	–0.02
Gastrectomized state	U.L.	56	17	0.0179	37.9	–0.05	–0.05	–0.05	–0.05	–0.05	0.05	0.05	0.05
	L.L.	29	11	0.0111	36.8	–0.25	–0.35	–0.40	–0.45	–0.45	–0.45	–0.35	–0.30
	Mean	45.1	14.3	0.0160	37.23	–0.16	–0.23	–0.24	–0.22	–0.18	–0.14	–0.09	–0.06
Total	U.L.	70	24	0.0200	38.2	0.05	0.05	0.05	0.05	0.15	0.15	0.25	0.30
	L.L.	15	11	0.0093	36.5	–0.50	–0.75	–0.75	–0.75	–0.70	–0.60	–0.45	–0.35
	Mean	42.1	15.5	0.0158	37.30	–0.15	–0.25	–0.29	–0.28	–0.21	–0.13	–0.06	–0.02

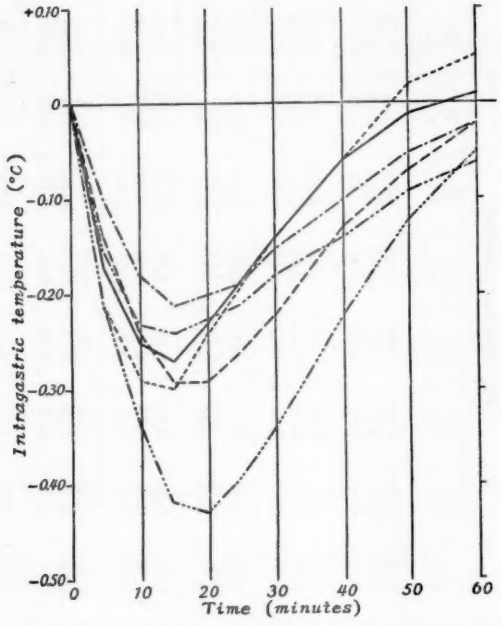

Fig. 1. The changes in the intragastric temperature after the injection of histamine in the groups of gastric (————) and duodenal ulcers (- - - - - - - - -), gastric cancer (— - — - —), cholelithiasis (— — — — —), and gastrectomized (— - - — - - —) and healthy states (— - - - — - - - —).

in the pulse pressure represent that the cutaneous blood vessels are dilated and the peripheral resistance is reduced. In addition, by the palpitation and increase in the pulse rate, it is certain that the blood flow increases. Therefore, the blood is cooled down peripherally at the body surface, which is exposed to the lower room temperature (11–24°C), and returns to the heart. It passes and is probably cooled through the lungs, returns to the heart again, and then flows into the vessels of the stomach. This process is repeated so that the intragastric temperature may fall. This assumption concerning the drop in the intragastric temperature is ascertained by the fact that, as mentioned above, both the onset and the recovery of the drop were preceded by those of the changes in the cardiovascular system, and the curves of these changes were mutually related. The intragastric temperature is in intimate relation with age, as shown in Fig. 2. In general the drop in the intragastric temperature was inversely proportional to the age regardless of the disease—the younger the age, the greater the drop. Next, the gastric free acidity reached the

TABLE III

The Upper (U.L.) and Lower Limits (L.L.) and Means of the Changes in the Intragastric Temperature at Each Time after the Injection of Histamine, when the 100 Individuals Tested are Classified according to Their Ages

Age group		Age years	Room temp. °C	Dose mg./kg.	Before inject. °C	After injection (minutes)							
						5 °C	10 °C	15 °C	20 °C	30 °C	40 °C	50 °C	60 °C
15–19 years	U.L.	19	21	0.0200	37.7	–0.20	–0.20	–0.20	–0.15	–0.05	0.05	0.10	0.15
	L.L.	15	12	0.0111	37.2	–0.45	–0.65	–0.70	–0.75	–0.70	–0.60	–0.45	–0.35
	Mean	17.2	15.2	0.0164	37.47	–0.27	–0.38	–0.43	–0.43	–0.35	–0.24	–0.16	–0.08
20–29 years	U.L.	29	23	0.0200	37.8	–0.05	–0.10	–0.10	–0.05	0.05	0.10	0.10	0.25
	L.L.	21	13	0.0100	36.8	–0.50	–0.75	–0.75	–0.75	–0.65	–0.45	–0.35	–0.30
	Mean	25.9	15.7	0.0164	37.41	–0.21	–0.37	–0.44	–0.45	–0.34	–0.22	–0.11	–0.03
30–39 years	U.L.	39	24	0.0178	38.2	–0.05	–0.10	–0.05	–0.05	0.05	0.10	0.10	0.15
	L.L.	30	12	0.0093	36.8	–0.35	–0.50	–0.50	–0.45	–0.35	–0.30	–0.25	–0.25
	Mean	33.2	15.1	0.0158	37.48	–0.19	–0.28	–0.30	–0.26	–0.16	–0.08	–0.02	0.01
40–49 years	U.L.	49	24	0.0179	38.1	0	0	0	0.05	0.15	0.15	0.20	0.25
	L.L.	41	13	0.0100	36.8	–0.40	–0.45	–0.50	–0.55	–0.45	–0.35	–0.30	–0.30
	Mean	44.8	15.2	0.0158	37.32	–0.14	–0.24	–0.26	–0.25	–0.19	–0.12	–0.05	–0.02
50–59 years	U.L.	59	24	0.0187	38.0	0	0	–0.05	0	0.10	0.15	0.25	0.30
	L.L.	50	11	0.0096	36.5	–0.25	–0.50	–0.55	–0.55	–0.55	–0.35	–0.30	–0.20
	Mean	54.3	15.5	0.0157	37.16	–0.12	–0.18	–0.22	–0.22	–0.16	–0.09	–0.04	0
60–70 years	U.L.	70	22	0.0175	37.5	0.05	0.05	0.05	0	0.05	0.05	0.15	0.10
	L.L.	60	11	0.0100	36.8	–0.15	–0.25	–0.35	–0.45	–0.40	–0.35	–0.30	–0.30
	Mean	63.7	16.8	0.0164	37.07	–0.05	–0.11	–0.16	–0.18	–0.18	–0.16	–0.11	–0.06
15–70 years	U.L.	70	24	0.0200	38.2	0.05	0.05	0.05	0.05	0.15	0.15	0.25	0.30
	L.L.	15	11	0.0093	36.5	–0.50	–0.75	–0.75	–0.75	–0.70	–0.60	–0.45	–0.35
	Mean	42.1	15.5	0.0158	37.30	–0.15	–0.25	–0.29	–0.28	–0.21	–0.13	–0.06	–0.02

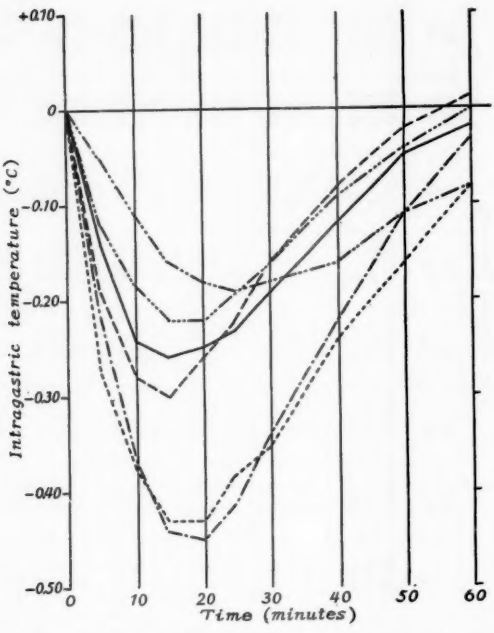

Fig. 2. The changes in the intragastric temperature after the injection of histamine in the various decades (15–19 years: - - - - - - - - - -; 20–29 years: — - — - —; 30–39 years: — — — — —; 40–49 years: ————; 50–59 years: — - - - — - - - —; and 60–70 years: — - - — - - —).

maximum increase at about 40 minutes after the injection but its increase varied according to the diseases (Fig. 4). As in the group of gastric ulcer, relatively chronic cases were included, the increase in the acidity was not marked. There seems to be no relation between the intragastric temperature and free acidity, because in the case of achylia (cancer etc.) and even in the case in which gastric resection was performed, the intragastric temperature fell as in the other cases, and because no parallelism was noticed between the curves of both changes.

Secondly, correlations among the seven factors, the maximum changes in the intragastric temperature, pulse rate, diastolic blood pressure and gastric free acidity, the age, the injected dose, and the room temperature, are considered to evaluate the relation among them quantitatively. Several simple, partial and multiple correlation coefficients are given in Table IV. The change in the intragastric temperature shows much higher values with those in the pulse rate and diastolic blood pressure than with the other factors in both the simple and the partial correlation coefficients

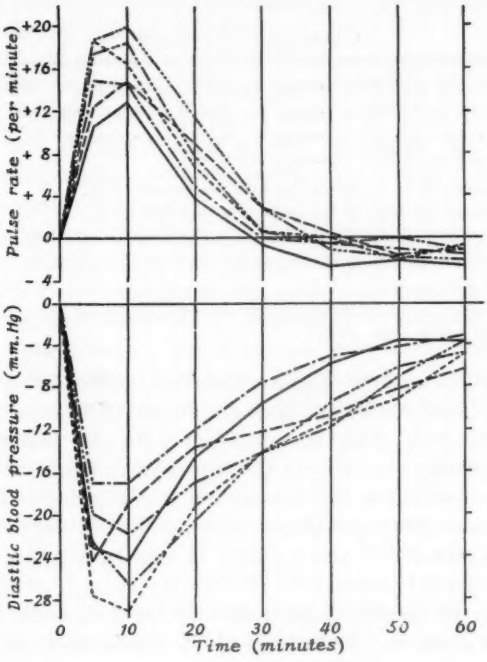

Fig. 3. The changes in the pulse rate and diastolic blood pressure after the injection of histamine as noted in Fig. 1.

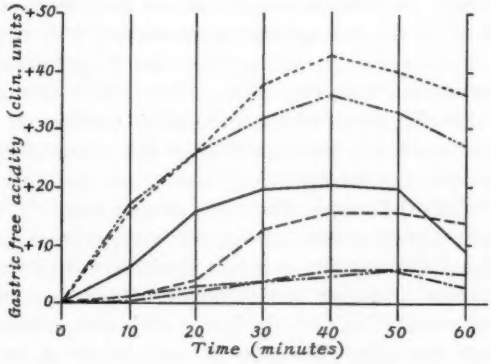

Fig. 4. The changes in the gastric free acidity after the injection of histamine as noted in Fig. 1.

TABLE IV

Correlation Coefficients

r_{TP} =	0.6076	r_{TD} =	0.3598	$r_{TP \cdot BFADR}$ =	0.4890	$r_{TD \cdot PBFAR}$ =	0.0392	$r_{T \cdot PB}$ =	0.7536
r_{TB} =	0.5931	r_{TR} =	0.1686	$r_{TB \cdot PFADR}$ =	0.4838	$r_{TR \cdot PBFAD}$ =	0.0572	$r_{T \cdot PBA}$ =	0.7717
r_{TF} =	0.2944	$r_{TA \cdot PB}$ =	−0.2528	$r_{TF \cdot PBADR}$ =	0.1227	$r_{FA \cdot TPBDR}$ =	−0.3925	$r_{T \cdot PBAD}$ =	0.7657
r_{TA} =	−0.5381	$r_{TD \cdot PB}$ =	0.0823	$r_{TA \cdot PBFDR}$ =	−0.1876				

T: The maximum drop in the intragastric temperature (°C).
P: The maximum increase in the pulse rate (per minute).
B: The maximum decrease in the diastolic blood pressure (absolute value in mm. Hg).
F: The maximum increase in the gastric free acidity (clinical units).
A: The age (years).
D: The injected dose of histamine hydrochloride (mg. per kg.).
R: The room temperature (°C).

and extends to 0.75 in the multiple correlation coefficient with the formers. Moreover, the latter coefficient does not exceed 0.78, even when the other factors are included. This is coincident with the above described assumption concerning the drop in the intragastric temperature and therefore, from the correlation the assumption is confirmed. The intragastric temperature also shows moderate negative simple correlation with the age, which represents the above stated inverse proportion between them. However, the partial correlation coefficient ($r_{TA \cdot PB}$), which is obtained by eliminating the factors of the pulse rate and diastolic blood pressure, becomes much smaller. Accordingly it is certain that the age-factor acts upon the intragastric temperature indirectly through the changes in the pulse rate and blood pressure. The similar tendency with the age is observed in the injected dose, though a weak correlation. Namely, the change in the intragastric temperature is not directly determined by the injected dose. According to the above described assumption concerning the drop in the intragastric temperature, it is expected that the lower the room temperature, the greater the drop becomes. However, there is no correlation between them. The effect of the other factors, for example, the dilatation of the cutaneous vessels, on the process of cooling of blood probably exceeds that of the room temperature. The correlation between the intragastric temperature and systolic blood pressure is smaller than 0.1 and entirely out of question. The partial correlation coefficient between the intragastric temperature and gastric free acidity eliminated the age-factor is not significant, but that between the gastric free acidity and age is significant. Therefore, the gastric free acidity shows no correlation with the intragastric temperature, but negative correlation with the age. Because, as mentioned above, the multiple correlation coefficient of the intragastric temperature with the other (six) factors is about 0.77, the further factors, which have influence on the

intragastric temperature, must exist actually. Then it is to be considered whether the disease acts as the factor.

Among the six groups, the patients and the healthy men (Table II), the injected dose and the room temperature showed no significant differences; and as to the age, significant ones were noticed except between healthy state and duodenal ulcer as well as among the remaining four. The intragastric temperature in the healthy men changed most remarkably in comparison with the patients, and its maximum drop was also greatest. Between the groups of duodenal ulcer and healthy state, the changes in the intragastric temperature were significantly different, while no significant differences in the changes in the pulse rate and diastolic blood pressure and in the age were noticed. Furthermore, the same tendency of the changes in the intragastric temperature was seen contrary to the changes in the cardiovascular system respectively in the three combinations: gastric and duodenal ulcers; gastric cancer and gastrectomized state; and healthy state and cholelithiasis. Therefore, it is certain that the disease is one of the factors, which have influence on the intragastric temperature. However, to estimate quantitatively its power and to make clear its mechanism are impossible in the present state of research.

Summary

Response of the intragastric temperature of men of various age groups, who were in healthy as well as several pathologic states, to subcutaneous injection of histamine was studied, in comparison with changes in the cardiovascular system and gastric juice; and the following facts were confirmed.

1. By histamine the intragastric temperature is lowered following increases in the pulse rate and pulse pressure and a drop in the diastolic blood pressure, which are accompanied by a flush of the face, heat sensation and palpitation.
2. After reaching the maximum drop, it recovers in a manner following the recoveries of the above mentioned changes.
3. It drops on account of flowing of the blood, which is cooled down at the body surface, into the gastric vessels; and the drop is determined chiefly by the changes in the pulse rate and diastolic blood pressure.
4. It is not related with the change in the gastric free acidity.
5. Both age and injected dose of histamine act upon the change in the intragastric temperature indirectly through those in the pulse rate and diastolic blood pressure.
6. Disease is one of the factors which influence the change in the intragastric temperature.
7. Room temperature has no correlation with the change in the

intragastric temperature.

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Studies on the Temperature of the Gastrointestinal Tract

Eighth Report

Influence of Cold Bathing on the Intragastric Temperature

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(Received for publication, September 4, 1952)

As in the second report[1], the influence of warm and hot bathing upon the intragastric temperature of men was studied, in this report that of cold bathing is presented.

Experimental

Methods and Materials

In the fasting state at least 4 hours after meals, an intragastric thermometer[2] was introduced into the stomach at 60 cm. from the incisor. About 30 minutes thereafter the intragastric temperature became almost constant, then cold bathing of tap-water was taken for 15 minutes. The bathing was performed according to the following three ways: partial immersion below the symphysis pubis; below the proc. ensiformis; and below the neck (the usual whole body bath). Temperature of the bath ranged between 22–24°C and that in the bath room, which faced northward, between 24–26°C. The intragastric temperature was measured continuously before and during bathing, and for 30 minutes after bathing in naked condition in the bath room. Gastric juice was aspirated at each 10 minutes through the Miller-Abbott's tube of the thermometer and the total and free acidities were determined as described in the fifth report[3]. On 15 healthy males, whose ages were from 24 to 28 years, 21 experiments were performed, each of the three ways being repeated 7 times. On the three men the bathings in the three different ways were carried out.

Results

The changes in the intragastric temperature before, during and after the cold bathings in the above described three ways are given in

TABLE I

The Changes in the Intragastric Temperature during and after the Cold Baths, below the Symphysis Pubis, the Proc. Ensiformis, and the Neck, for 15 Minutes at 22–24°C

Part immersed	No.	Water temp. °C	Room temp. °C	Before bathing °C	During bathing (minutes)				After bathing (minutes)				
					4 °C	8 °C	12 °C	15 °C	4 °C	8 °C	16 °C	24 °C	30 °C
Below the symphysis pubis	1	23.5	26.0	37.7	0	0.10	0	0.10	−0.05	−0.20	−0.35	−0.30	−0.30
	2	22.0	25.0	37.4	0.05	0.10	0.15	0.20	0.20	0.25	0.30	0.25	0.25
	3	22.0	25.0	37.3	0	0.05	0.15	0.15	0.05	0.20	0.15	0.10	0.05
	4	22.0	24.0	37.4	−0.10	0.05	0.20	0.25	0.15	0.05	−0.05	−0.10	−0.05
	5	23.2	25.0	37.8	0	0.10	0.10	0.10	−0.10	−0.25	−0.30	−0.45	−0.45
	6	23.3	26.0	37.6	0	0.05	0.10	0.05	0	0.05	0	−0.05	−0.10
	7	23.3	25.0	37.8	0	0.10	0.10	0.20	0	0.05	0	−0.05	−0.05
	Sum	159.3	176.0	263.0	−0.05	0.55	0.80	1.05	0.25	0.15	−0.25	−0.60	−0.65
	Mean	22.8	25.1	37.57	−0.01	0.08	0.11	0.16	0.04	0.02	−0.04	−0.08	−0.09
Below the proc. ensiformis	1	23.0	25.0	37.3	0.05	0.05	0.05	0.15	0.05	−0.05	−0.25	−0.25	−0.30
	2	22.0	26.0	37.4	0	0.10	0.15	0.30	0.25	0.30	0.15	0.05	0.05
	3	22.0	24.0	37.3	0	−0.05	−0.15	−0.30	−0.35	−0.30	−0.35	−0.35	−0.35
	8	23.0	26.0	37.3	0.10	0.25	0.35	0.40	0.25	0.15	0.10	0	−0.05
	9	23.0	26.0	37.4	0.15	0.30	0.25	0.20	0.10	0.10	−0.05	−0.05	−0.10
	10	24.0	26.0	37.3	−0.10	−0.05	−0.05	0	−0.15	−0.15	−0.25	−0.25	−0.30
	11	24.0	26.0	37.3	−0.05	−0.10	−0.10	−0.15	−0.05	−0.20	−0.10	−0.15	−0.15
	Sum	161.0	179.0	261.3	0.15	0.50	0.50	0.60	0.10	−0.20	−0.70	−1.00	−1.20
	Mean	23.0	25.6	37.33	0.02	0.07	0.07	0.08	0.01	−0.03	−0.10	−0.14	−0.17
Below the neck	1	22.5	24.0	37.3	−0.05	−0.05	−0.25	−0.40	−0.75	−0.95	−1.15	−1.10	−1.10
	2	22.0	24.0	37.4	−0.05	0	−0.05	−0.05	−0.15	−0.25	−0.45	−0.55	−0.60
	3	22.5	26.0	37.2	0.05	−0.05	−0.15	−0.25	−0.50	−0.65	−0.80	−0.85	−0.85
	12	22.5	26.0	37.0	−0.05	0.05	−0.05	−0.15	−0.40	−0.65	−0.90	−0.85	−0.85
	13	23.0	24.2	37.5	0	0.10	0.05	0	−0.05	−0.05	0.05	−0.05	0
	14	23.0	25.0	37.3	0.05	0.10	0.05	0	−0.40	−0.50	−0.45	−0.35	−0.30
	15	22.1	24.8	37.8	−0.05	0.05	0.05	0.10	0	−0.10	−0.15	−0.15	−0.20
	Sum	157.6	174.0	261.5	−0.10	0.20	−0.35	−0.75	−2.25	−3.15	−3.85	−3.90	−3.90
	Mean	22.5	24.9	37.36	−0.04	0.03	−0.05	−0.11	−0.32	−0.45	−0.55	−0.56	−0.56

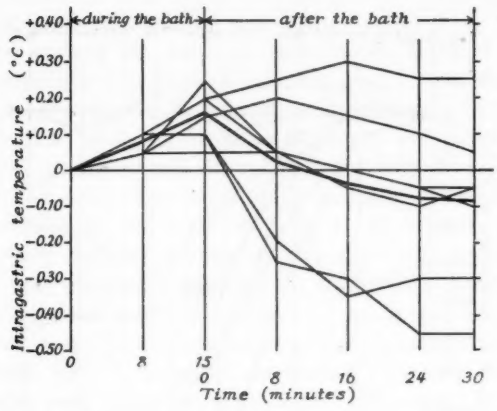

Fig. 1. The changes in the intragastric temperature during and after the cold bath below the symphysis pubis for 15 minutes at 22–24°C. The thick line represents the mean.

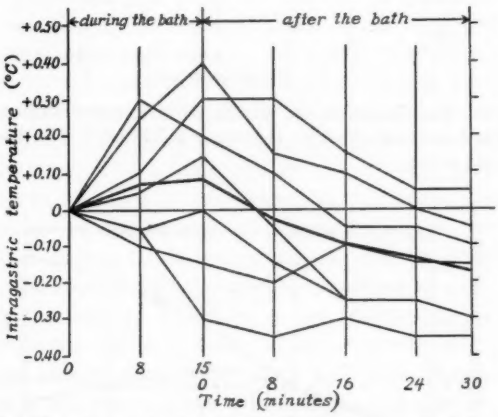

Fig. 2. The changes in the intragastric temperature during and after the cold bath below the proc. ensiformis for 15 minutes at 22–24°C. The thick line represents the mean.

Table I and illustrated in Figures 1, 2 and 3 respectively. The means of the changes in the gastric free acidity are shown in Fig. 4.

Discussion

During the bath below the symphysis (Fig. 1), the intragstric temperature continued to rise in all the cases and reached the maximum rise of

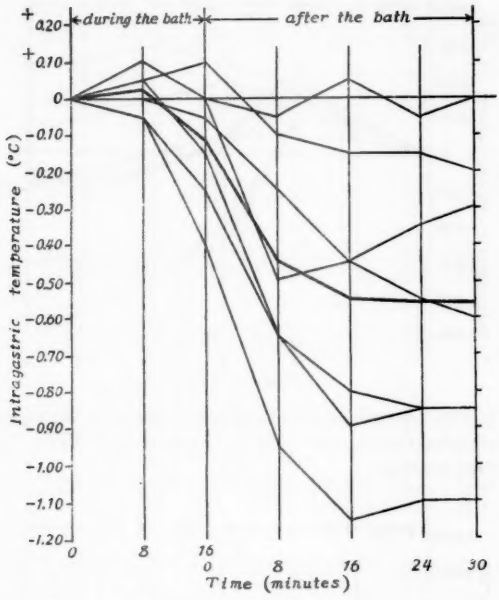

Fig. 3. The changes in the intragastric temperature during and after the cold bath below the neck for 15 minutes at 22–24°C. The thick line represents the mean.

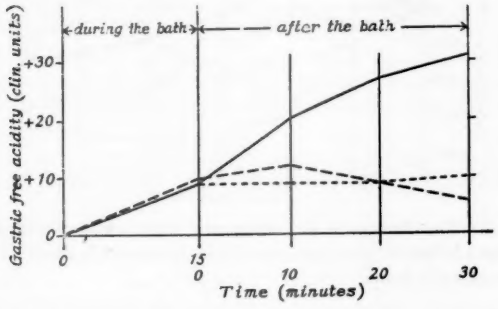

Fig. 4. The means of the changes in the gastric free acidity during and after the cold baths for 15 minutes at 22–24°C, below the symphysis pubis (— — — —), the proc. ensiformis (- - - - - - - - - - -), and the neck (————).

0.16°C on an average, when bathing was finished. After bathing it began to fall except in one case. Though its fall was relatively marked only in two cases, in a greater part it merely recovered to the level before

bathing and became −0.09°C at 30 minutes after bathing. As the rise during bathing was statistically significant contrary to the fall after bathing, in this bathing the rise was regarded as the chief change in the intragastric temperature in spite of cold bathing. Next, during the bath below the neck (Fig. 3), the intragastric temperature at first rose in five cases within 0.10°C, and thereafter it bagan to fall in every case, becoming −0.11°C on an average when bathing was finished. After bathing it continued to fall more remarkably for 20 minutes, and became −0.56°C, remaining thereafter at the same level up to 30 minutes after bathing. This fall was very manifest except in two cases and its maximum was −1.15°C. It was significant contrary to the change during bathing and thus is regarded as the true fall by the cold bathing. Therefore, in this bathing the fall was the chief change in the intragastric temperature. During the bath below the proc. ensiformis (Fig. 2), the intragastric temperature also rose as mentioned above. However, its rise was not so uniform as in the bath below the symphysis. In a part it rose even more markedly in spite of the bath in which the part greater than the bath below the symphysis was immersed, but in the other it began to fall from the first. Consequently the range of its change, when bathing was finished, was broad and scattered between a rise of 0.40°C and a fall of −0.30°C. Though after bathing it fell becoming after 30 minutes −0.17°C on an average, its fall essentially resembled to that in the bath below the symphysis. It merely recovered to the level before bathing, and the changes both during and after bathing were not significant. In this bathing the individual variations, which appeared in the changes in the intragastric temperature, were manifest as compared to the baths stated above and a definite tendency of the change could not be found.

As described above, the intragastric temperature at first rose during cold bathing. In general this rise became manifest as well as long lasting inversely proportionally to the area to be immersed, and in the bath below the symphysis this rise was actually significant. Following this the intragastric temperature fell. This fall was distinguished in two groups: one was the seeming fall which appeared only by recovering of the rise above stated; and the other was the true fall by the cold bath. In general the former was observed when the area to be immersed was small as in the baths below the symphysis and proc. ensiformis, and the latter when the area was wide as in the bath below the neck. Furthermore, there were some cases in which the preceding rises were so covered with the true falls that the intragastric temperature fell from the beginning of the bath, especially in the bath below the neck. However, it is certain that the intragastric temperature at first, as a rule, rose by the cold bath.

It is interesting that in spite of the cold bathing the intragastric

temperature at first rises. This is considered to be the self-defense mechanism of the body to the cold. For the genesis of this rise, as the heat production in the body cannot occur within such a short time to be of so great an extent, changes in the distribution of blood or in the blood flow in the body, especially in the splanchnic viscera, caused reflectively by the cold bath, are probably the important factors. These changes, which are under the control of the autonomic nervous system, may be related partly with the mechanism, expressed as the " splanchno-peripheral balance." This rise is also interesting when compared to the fact that by the warm bath of 37°C the intragastric temperature at first falls and then rises as reported in the second report[1]. The true fall, not the seeming fall, following this rise is due to that the power to cool down is so strong or so lasting as to exceed the limit of the self-defense mechanism; and this fall is perhaps produced by the flowing of the blood, cooled peripherally at the body surface by the cold water, into the gastric vessels. This fall is, as mentioned above, more marked after bathing, especially for the first 20 minutes, than during bathing. It is due to changes in the body reactions produced by disappearance of the cold stimulation and is probably related closely with the self-defense mechanism, particularly with changes in the blood flow in the body.

Individual variation appears in the change in the intragastric temperature by the cold bath. There are men whose intragastric temperature falls easily and greatly by the cold baths in the three ways above described as Nos. 1 and 3 in Table I and the others inverse to the formers as No. 2. The appearance of the individual variation also seems to be in intimate relation with the area to be immersed. When the area is apparently wide or small as in the bath below the neck or below the symphysis, the change in the intragastric temperature is relatively so uniform that certain significant change, i.e., the fall or rise, is observed. Contrary to the above, when a moderate part of the body is immersed as in the bath below the proc. ensiformis, the change is so variable by individuals that its distribution shows a very wide range. Therefore, individual variation tends to appear manifestly in the bath in which the power to raise the intragastric temperature is almost equal to that to lower.

The gastric free acidity showed no significant change by the baths below the symphysis and the proc. ensiformis, because there were considerable cases in which it did not increase (Fig. 4). However, by the bath below the neck it significantly increased showing the average rise of 30.9 clinical units at 30 minutes after bathing, though only one case showed no change. The volume of the aspirated juice also tended to increase in the latter. Therefore, the gastric secretion increases by the

cold bath. However, no notable relation between the change in the intragastric temperature and that in the gastric secretion was seen.

Summary

Changes in the intragastric temperature of healthy men by cold bathing were studied, varying the part to be immersed, and the following facts were confirmed.

1. The intragastric temperature at first rises by cold bathing. This rise is inversely proportional to the area to be immersed.
2. Following this rise it falls and in the fall two types are distinguished —one is the seeming fall due to recovery of the rise and the other the true fall by the cold bath. The former appears when the area to be immersed is small and the latter when the area is wide.
3. In some cases it falls from the beginning of the bath, because the preceding rise is covered with the true fall.
4. There are considerable individual variations in the above stated rise and fall.
5. Appearance of this variation is also in intimate relation with the area to be immersed.
6. The gastric secretion is increased by the cold bath.

References

1) Masuda and Ohara, Tohoku J. Exp. Med., 1951, **54**, 363.
2) Masuda, *ibid.*, 1951, **54**, 355.
3) Masuda, Ohara and Katsura, *ibid.*, 1953, **57**, 129.

The Tohoku Journal of Experimental Medicine, Vol. 58, No. 1, 1953

Newborn Virus Pneumonitis (Type Sendai)
I. The Clinical Observation

By

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(Received for publication, June 5, 1953)

For about two months from March, 1952, seventeen newborns suffered from one to another of the following symptoms and eleven out of them died. The clinical characteristics of this pneumonitis of newborns were as follows: high contagiousness, high mortality up to 64.7%, slight symptoms in the premature infants, sudden onset without any prodromal symptoms; high fever (38.5-41.8°C); respiratory distress, cyanosis, increased jaundice, rhinopharyngitis, sweating, marked leucocytosis (20,000–40,000), especially due to neutrophilia (60–80%) from the beginning of the illness, high grade of anemia in the reconvalescence stadium; slight pathological findings on the chest, though diffuse shadows were obviously found in the lung fields on the roentgenogram; and no inclusion bodies showed in throat smears. Both the Hirst-test and cold hemoagglutination test were negative. All kinds of antibiotics were ineffective.

This newborn virus pneumonitis is diagnosed differentially from the pneumonitis described by Nitschke, Adams and others. This pneumonitis can be clinically concluded to be a new type of newborn pneumonitis and is termed as "Newborn Virus Pneumonitis (type Sendai)."

Recently in March of this year we could find a new sporadic case of the newborn pneumonitis, which showed the same clinical symptoms as previous cases and recovered entirely from them, and the virus isolated from this case has at all the same characteristic points as above "type Sendai." (See page 62 and 82)

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Studies on the Temperature of the Gastrointestinal Tract

Ninth Report

Relation of the Intragastric Temperature to Gastric Secretion

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(Received for publication, September 4, 1952)

The response of the intragastric temperature to gastric secretion is an interesting problem both physiologically and clinically. To study this problem in man it is necessary to observe both the normal and the pathologic stomachs, which include hyperacidity observed in gastric and duodenal ulcers, etc. and hypo- or anacidity in gastric cancer and cholelithiasis, etc., as well as the gastrectomized state. In addition, to attempt various methods to stimulate gastric secretion is important. When the response of the intragastric temperature to various drugs, especially histamine, was studied previously,[1)-3)] some observations on gastric secretion were presented. In this report gastric secretion which originates only by the introducing of an intragastric thermometer is studied.

Experimental

Methods and Materials

In a fasting and basal condition, in most cases before breakfast, an intragastric thermometer[4)] was introduced into the stomach at 60 cm. from the incisor. Then the intragastric temperature of 120 individuals including 94 males and 26 females, who are listed in Table I, was continuously measured for 30 minutes, simultaneously with aspiration of the gastric juice in an interval of 10 minutes through the Miller-Abbott's tube of the thermometer. The aspirated gastric juice was examined for the free and total acidities as reported previously[1)]. If hydrochloric acid was present in the juice aspirated immediately following the introduction of the thermometer, the experiment was repeated on another day to obtain the case in which the acid was absent. The room temperature ranged between 11 and 24°C.

TABLE I

Age and Disease or State of 120 Individuals Tested

Disease or State	15–19 years	20–29 years	30–39 years	40–49 years	50–59 years	60–70 years	Total
Healthy state	4	37	3	1	5	0	50
Gastric ulcer	0	3	4	4	7	0	18
Duodenal ulcer	1	3	2	4	0	0	10
Gastric cancer	0	0	5	9	6	3	23
Cholelithiasis	0	2	3	1	5	1	12
Gastrectomized state	0	1	0	4	2	0	7
Total	5	46	17	23	25	4	120

Results

The data for the changes in the intragastric temperature and gastric free acidity after the introduction of the thermometer in the patients and

TABLE II

The Upper (U.L.) and Lower Limits (L.L.) and Means of the Changes in the Intragastric Temperature and Gastric Free Acidity at Each Time after Introducing of the Thermometer into the Stomach

Disease or state	No.		Age years	Intragastric temperature (minutes) 0 °C	5 °C	10 °C	15 °C	20 °C	25 °C	30 °C	Gastric free acidity 0 c.u.	10 c.u.	20 c.u.	30 c.u.
Healthy state	50	U.L.	56	38.0	0.05	0.10	0.10	0.10	0.10	0.10	0	18	60	64
		L.L.	18	36.7	–0.10	–0.10	–0.10	–0.10	–0.10	–0.10	0	0	0	0
		Mean	29.2	37.37	0	0.02	0.02	0.02	0.01	0	0	1.8	5.9	9.3
Gastric ulcer	18	U.L.	58	37.9	0.05	0.10	0.10	0.15	0.15	0.15	0	20	36	50
		L.L.	27	36.4	–0.05	–0.05	–0.05	–0.05	–0.10	–0.10	0	0	0	0
		Mean	43.0	37.03	0.01	0.05	0.05	0.06	0.06	0.05	0	5.4	12.4	17.7
Duodenal ulcer	10	U.L.	45	37.7	0.05	0.10	0.15	0.15	0.15	0.15	0	20	36	50
		L.L.	15	36.6	0	–0.05	–0.05	–0.05	–0.10	–0.10	0	0	0	0
		Mean	31.6	37.24	0.01	0.04	0.06	0.06	0.05	0.05	0	6.6	14.2	17.4
Gastric cancer	23	U.L.	69	38.2	0.05	0.10	0.10	0.10	0.15	0.15	0	20	24	30
		L.L.	32	36.7	–0.05	–0.05	–0.10	–0.10	–0.10	–0.10	0	0	0	0
		Mean	47.4	37.33	0.01	0.02	0.03	0.04	0.03	0.03	0	0.9	1.5	2.0
Cholelithiasis	12	U.L.	70	37.9	0.05	0.05	0.10	0.15	0.15	0.15	0	0	16	30
		L.L.	21	36.9	–0.05	–0.05	–0.10	–0.10	–0.15	–0.15	0	0	0	0
		Mean	45.0	37.37	0.01	0.02	0.02	0.04	0.03	0.03	0	0	1.8	3.3
Gastrectomized state	7	U.L.	56	37.9	0.05	0.05	0.05	0.10	0.10	0.10	0	0	0	0
		L.L.	29	36.8	–0.05	–0.05	–0.05	–0.05	–0.05	–0.05	0	0	0	0
		Mean	45.1	37.30	0	0.01	0.02	0.04	0.04	0.02	0	0	0	0
Total	120	U.L.	70	38.2	0.05	0.10	0.15	0.15	0.15	0.15	0	20	60	64
		L.L.	15	36.4	–0.10	–0.10	–0.10	–0.10	–0.15	–0.15	0	0	0	0
		Mean	37.5	37.30	0	0.02	0.03	0.03	0.03	0.02	0	2.3	6.0	8.7

c.u.: Clinical Units.

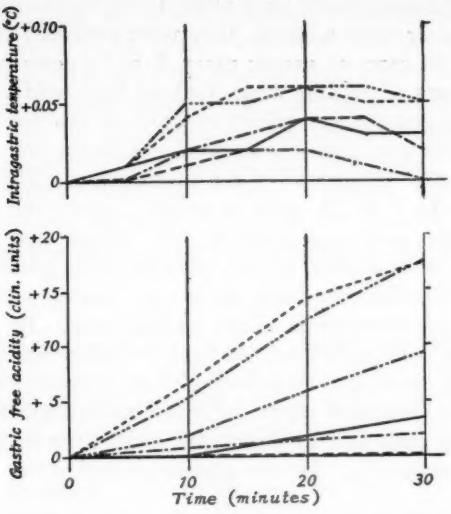

Fig. 1. The changes in the intragastric temperature and gastric free acidity after introducing of the thermometer into the stomach in the groups of gastric (— - - - — - - - —) and duodenal ulcers (- - - - - - - - -), gastric cancer (— - — - — - —), cholelithiasis (————), and gastrectomized (— — — —) and healthy states (— - - — - - — - - —).

healthy men are shown in Table II and Fig. 1. In Table II the upper and lower limits and means of the changes at each time are given and in Fig. 1 the means are plotted.

Discussion

The intragastric temperature after introducing of the thermometer was slightly elevated on an average in the patients as well in the healthy men (Fig. 1). However, those average rises were within only 0.06°C and in individual cases many were inversely lowered. Both the rise and the drop were approximately of the same degree, within ±0.15°C (Table II), and the cases which showed no change were also observed. Therefore, the intragastric temperature changed individually at random within ±0.15°C and the change was not noticed as statistically significant. The change showed no significant difference according to the patients and healthy men. Additionally, the intragastric temperature following the introduction of the thermometer was lower in ulcers and significant in gastric ulcer than in the other cases (Table II). This indicates that the body temperature is low in the patients with gastric and duodenal ulcers.

As in the experiment, the cases in which free hydrochloric acid was

absent in the aspirated gastric juice immediately following the introduction of the thermometer were selected, they were regarded to be in secretory rest. In 11 of 18 cases of gastric ulcer, 8 of 10 cases of duodenal ulcer and 19 of 50 cases of healthy state, hydrochloric acid was secreted after the introducing, and the free acidity reached an average rise of 18 clinical units in the patients of gastric and duodenal ulcers and of 9 units in the healthy men at 30 minutes after the introducing. Those changes were all significant. In 2 of 23 cases of gastric cancer and 2 of 12 cases of cholelithiasis, the acid was secreted, but it was not significant. The changes in the free acidity of the patients with gastric and duodenal ulcers differed significantly from those with gastric cancer and cholelithiasis, though not from those of the healthy men. In 7 cases, in which gastric resection was performed, no acid secretion was noticed. Therefore, the acid secretion after introducing of the thermometer in the patients with gastric and duodenal ulcers increased pathologically in comparison with the healthy men and in those with gastric cancer and cholelithiasis decreased pathologically. In the gastrectomized state, as a rule, it did not occur.

As mentioned above, the gastric free acidity changed according to the patients and the healthy men, contrary to the intragastric temperature which did not change significantly. In individual cases, a rise in the acidity corresponded not to a certain change in the temperature, but to both the rise and the drop at random. Moreover, a correlation coefficient between the rise in the acidity and the change in the temperature was only 0.124 (120 cases) and this is not regarded as significant. Accordingly, there seems to be no significant relation between the change in the acidity due to the introducing of the thermometer and that in the temperature.

The relation between the change in the intragastric temperature after injection of various drugs and that in the gastric free acidity was presented in the fifth, sixth and seventh reports[1)-3)]. Especially in the seventh report[3)], histamine, the most powerful stimulant for gastric secretion, was injected to patients as well as healthy men as in this report. In the cases of anacidity of gastric cancer and cholelithiasis and even in the cases in which gastric resection was performed, the intragastric temperature was lowered as in the cases of hyperacidity of ulcers. Moreover, the correlation coefficient between the change in the temperature and that in the acidity was not significant. Therefore, there seems to be no significant relation between the change in the acidity after the injection of drugs and that in the temperature.

From the discussion given above, it is certain that gastric secretion both originated by only introducing of the thermometer and stimulated

by injection of histamine, in cases of hyper-, normo-, hypo- and anacidities observed in the patients with gastric and duodenal ulcers, gastric cancer and cholelithiasis as well as in the healthy and gastrectomized men, has no significant relation to the change in the intragastric temperature. However, it must be kept in mind that the thermometer used in the experiments has a certain sensitivity (0.025°C) and the change within this limit cannot be detectable. Nevertheless such a minute change is, at least in the living body, not significant, because the intragastric temperature changes at random within ±0.15°C regardless of gastric secretion.

Summary

Gastric secretion, originated by only introducing of a thermometer into the stomach, in healthy and several pathologic states was studied, simultaneously with the change in the intragastric temperature; and the following facts were confirmed making reference to the results reported previously[1)-3)].

1. Gastric secretion both originated by only introducing of the thermometer and stimulated by the injection of drugs, especially histamine, has no significant relation to the change in the intragastric temperature.

2. The intragastric temperature does not change significantly by introducing of the thermometer regardless of the patients and healthy men.

3. Gastric secretion after introducing of the thermometer increases pathologically in gastric and duodenal ulcers, and decreases in gastric cancer and cholelithiasis in comparison with healthy state, while it does not occur, as a rule, in gastrectomized state.

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1) Masuda, Ohara and Katsura, Tohoku J. Exp. Med., 1953, **57**, 129.
2) Masuda, Ohara and Katsura, *ibid.*, 1953, **57**, 137.
3) Masuda, *ibid.*, 1953, **58**, 39.
4) Masuda, *ibid.*, 1951, **54**, 355.

Newborn Virus Pneumonitis (Type Sendai)
II. The Isolation of A New Virus

By

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(Received for publication, June 5, 1953)

In the spring of 1952, an outbreak of newborn pnemonitis occurred in this University Hospital. (See page 56)

In our laboratory, the isolation of virus from 5 autopsic materials was carried out by nasal instillation of lung suspensions to mice. All of the mice died between 5 to 7 days and presented a consolidation of lungs, resembling that of influenza. The pathological findings of lungs were similar to that of newborns. (See page 82)

After adaptation to mice, they could be cultivated in amniotic and allantoic cavity of fertile eggs, and after subsequent passage, hemagglutinin (HA) was proved in both cavities. HA was adsorbed to and eluted from chicken erythrocytes. Heat stablity of HA was so feeble when compared to another virus, belonging to MNI. Receptor gradient of the virus was arranged between NDV and FMI.

HA-inhibition test was performed by several specimens of monovalent rooster serum, i.e. of this virus (Fushimi), Mumps (Enders), Newcastle (Fukumi), influenza A (PR8 and WS), A′ (FMI, Lépine and Matsumoto), B (Lee, Seattle and T14) and C (1233). No other serum could inhibit this HA, except the correspondent serum. Beside this, Akitsugu and Tochigi strains, both isolated from adult's influenza in other laboratories were proved to possess the same antigenic structure with this virus.

Recently we could find again a new sporadic case, and isolated the same virus from throat and the elevation of antibody against this virus in paired serum of this patient was proved by HA-inhibition test. Further research proved the enzootic nature of this virus i.e. the same virus was isolated from normal laboratory mice. But all of mice examined have no antibody against this virus.

Intranasal instillation of the virus to a volunteer caused a fever of the saddleback type and high elevation of antibody. The virus was also revovered from throat 2 times after onset.

The purification studies of the virus by the supercentrifuge revealed a spherical particle 150 to 200 mμ in size.

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Theory of Blurring of X-Ray Images and Occurrence of Obstructive Shadows in Rotatory Cross Section Radiography

(Studies on Rotatography. 9th Report)

By

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Concerning the mechanism accounting for the occurrence of blurred images or obstructive shadows in Rotatory Cross Section Radiography,[1] there have been published no thorough investigations so far. Bacause of its importance as the groundwork in this field we have studied on this thema theoretically as well as experimentally. We shall discuss about this thema in reference to the three cases: a) taking a Cross Section Radiogram showing a point which is placed beyond the plane to be cross-sectioned, b) a curved line or plane which is involved in a plane paralleled to the plane to be cross-sectioned c) and a curved line or plane involved in a plane inclined to the plane to be cross-sectioned.

I. A Point Placed beyond the Plane to be Cross-sectioned. (Fig. 1)

A small disc 0.1 mm. thick was subjected to the experiment. In Rotatory Cross Section Radiography, a point, which is involved in the cross section, namely, the plane g_1 is imaged as one point. A point placed beyond this plane, however, is blurred into locus of a circle. (Figiure, not given) (Gebauer,[2] Takahashi,[3] Vieten[4]).

In this case the radius R of the circle counts:

$$R=\frac{(a+b)\cdot e}{a\ \tan\varphi - e}$$ (Takahashi,[2] Vieten[3])

a: target-body table-distance
b: body table-film table-distance
φ: inclination of the central x-ray to the horizontal film surface
e: distance between plane g_2 and plane g_1

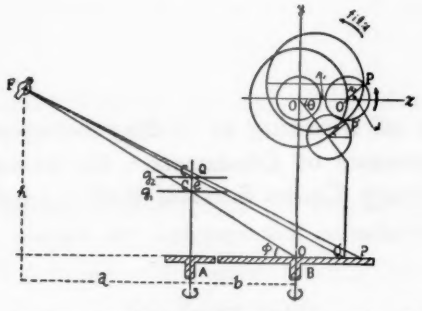

Fig. 1. Diagram showing a Rotatory Cross Section Radiogram of a point. Bottom left: elevation Top right: plan. F: focus of the X-ray tube, A, B: rotation table.

The position of the center of this circle is determined in the following way.

The rotation center C of plane g_1 is projected on the rotation center O of the film as shown at the top right of Fig. 1, while the rotation center C_1 of the plane g_2 is imaged as point O′ on the film. Point Q on plane g_2 is projected on the film and imaged as point P. Rotating around Point O, point O′ itself is encircled by the rotating point P. Let OO′ be named abscissa x, and a line, intersected at a right angle with OO′ at O, be ordinate y. Let the inclination of OP to abszissa x be α. Be the length of $\overline{OO'}$ r_1 and that of O′ P, r_2. Let us first suppose that only the circle r_2 rotates around O counterclockwise at an angle velocity of θ and that the film is fixed stationary. Then the point (x, y) is determined by the following formulas:

$$x = r_1 + r_2 \cdot \cos(\theta + \alpha)$$
$$y = r_2 \cdot \sin(\theta + \alpha)$$

Next, suppose two new axes which rotate around the origin O counterclockwise at the angle velocity θ. Then the point (X, Y) referred to new axes are:

$$x = X \cos\theta - Y \sin\theta$$
$$y = X \sin\theta + Y \cos\theta$$

Elminate x and y from the above formulas, and there will be obtained

$$(X - r_2 \cos\alpha)^2 + (Y - r_2 \sin\alpha)^2 = r_1^2 \quad \ldots\ldots\ldots\ldots 1$$

As this is the equation representing a circle, the coordinates of the center of a circle in this case are the point R ($r_2 \cos\alpha$, $r_2 \sin\alpha$).

If the center of this circle is required in drawing a figure, construct the parallelogram O O′ P R. The vertex R is what is required.

II. In the Case of a Line or Plane Involved in Plane g_2 which is Parallel to the Plane to be Cross-sectioned

A line or plane 0.1 mm. thick was used in the experiment.

a) A line (Fig. 2)

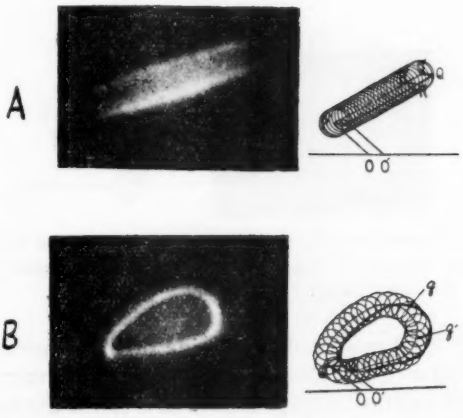

Fig. 2. A line involved in a plane paralleled to the cross section. Left. A. Cross Section Radiogram of a straight line showing a line shadow. Left. B. Cross Section Radiogram of a closed curved line showing a line shadow. A. right Analysis of the X-ray image A on the left. PQ: normal X-ray image of a straight line. R: a point on the line PQ. O: rotationcenter of the film. O′: Projection of the rotation center of the plane on which a straight line is placed. B. right Analysis of the X-ray image B on the left. q: normal X-ray image of a curved line.

A line may be considered as one-dimensional arrangement of numerous points. When radiographed normally, it is imaged on the film as the line P Q. Any point R on this line P Q blurs into a circle with the length of radius O O′ and with the center corresponding to the vertex R_1 of Parallelogram O O′ R R_1.

The center R_1 draws locus P_1 Q_1, which is parallel to the line P Q. Therefore the line P Q blurs as numerous circles with their centers arranged on the line P_1 Q_1. The circles intersect with one another. The outer most brim of these circles corresponding to their envelop is deepest in shade. Therefore a line placed in the plane g_2 paralleled to the cross-sectioned one g_1 is crossgraphed as two lines parallel to each other.....2

The distance between the images of the two lines is R. These lines are different in their apearance from the nucleus shadow.[5] Accordingly we shall call each of these a line shadow.

b) A plane (Fig. 3)

A plane is, so to speak, two-dimensional arrangement of lines. The blurred circle of a point on the perimeter situated inside at the distance of Δ R from the contour of the plane in question intersects with the circle of one on the contour of the plane. So the density of the blurred area is made even from the outer side to the inner one, and becomes homogenous.

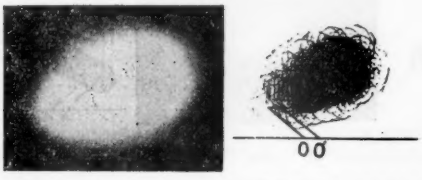

Fig. 3. A plane involved in a plane paralleled to the cross section. Left: Cross Section Radiogram of a plane showing a nucleus shadow. Right: Analysis of the X-ray image.

In the zone 2R broad and just inside of the contour of the blurred area there remains a deeper shadow, caused by the concurrence of blurred circles at the center of the image. This area is called the nucleus shadow.[5] 3

III. In the Case of a Line or Plane which is Involved in a Plane Inclined to the Plane to be Cross-sectioned

A line or plane 0.1 mm. thick was used in the experiment.

a) A line (Fig. 4)

The line in this case is to be considered as an array of points in numerous planes piled at the distance of the variable e from the plane g_1.

Therefore the length of Radius R of a blurred circle is variable according to the position of the point. Furthermore the center of a circle transfers its position according to the length of the radius as shown in Fig. 1.

Therefore when a straight line is placed inclined to the plane to be cross-sectioned, the blurred shadow is imaged as two straight lines intersecting with each other. The intersecting point corresponds to the cross section of the line.....4

The intersecting angle represents the inclination of the line to the plane cross-sectioned.

When a plane involving a closed curved line f is inclined to the plane to be cross-sectioned and is rotatory-crossgraphed, this curved line is imaged as a figure of two closed curves in semicircles. (Fig. 5) This

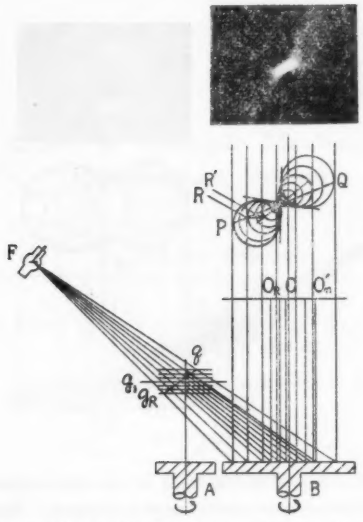

Fig. 4. A straight line inclined to the cross section. Bottom left: diagram of the elevation showing the analysis of the X-ray image. q: a straight line to be imaged. Middle right: diagram of the plan showing analysis of the X-ray image. PQ: normal X-ray image of the line q. Top right: Cross Section Radiogram of the line q, which is placed with the same inclination as shown in the elevation. A nodal point showing the cross section of the line.

is another case of the line shadow. They are connected with each other at each of their sharpened ends.

These two nodal points also correspond to the cross-sectioned points of the closed curved line.

b) A plane (Fig. 6)

When a plane inclines to the plane to be traversed, it is blurred as shown in Fig. 6. The blurred x-ray image is homogenous in density and leaves a nucleus shadow at its center.

Summary

The mechanism of occurrence of blurred images or obstructive shadows in Rotatory Cross Section Radiography has been analysed from the theoretical as well as the experimental point of view, and the following are the conclusions reached.

1. A point beyond the plane to be traversed is blurred into a locus of a circle:

$$(X-r_2 \cos \alpha)^2+(Y-r_2 \sin \alpha)^2=r_1^2.$$

The center of this circle is determined as co-ordinates ($r_2 \cos \alpha$, r_2

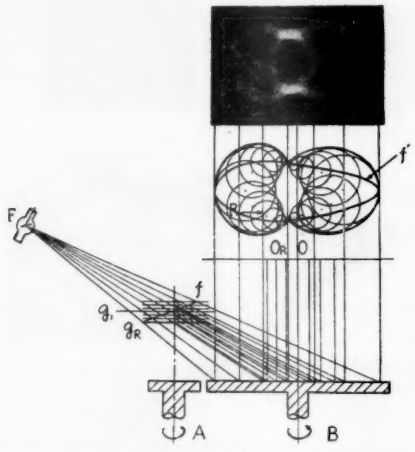

Fig. 5. A closed curved line inclined to the cross section. Bottom left: Diagram of the elevation f: a curved line to be imaged. Middle right: diagram of the plan. f: normal X-ray image of the line f. Top right: Cross Section Radiogram of the line f. Two nodal points showing the cross section.

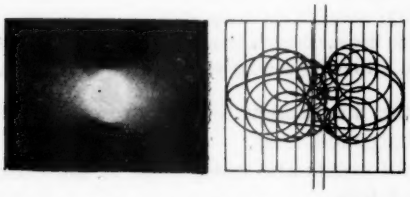

Fig. 6. A plane inclined to the cross section. Left: Cross Section Radiogram of the plane showing a nucleus shadow. Right: analysis of the X-ray image.

sin α) of this formula.

2. When a line is blurred, the result is an image of two characteristic shaodws. This was called a line shadow.

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Two Kinds of Scotopic Mechanisms in the Human Retina

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Introduction

In the duplicity theory it is assumed that scotopic and photopic vision are mediated by rods and cones respectively. Although the evidences have steadily accumulated in favor of the idea of two separate modes of vision,[1-14] it is possible that the cones can, in certain cases, function to some extent in night vision, retaining some of the attributes of the more primitive mechanism from which they are evolved.[15-16]

The elaborate work by Polyak[17] has directed our attention to the fact that besides the photoreceptor cells, there is a host of other structures, far too numerous and peculiarly organized to be ignored in the retina. We have now strong evidences that the cones and the rods converge into a final common path.[17-18] If the cones and the rods function so separately as the duplicity theory assumes, the interconnections in the "intermediate zone"[19-20] are difficult to understand.

Motokawa and his associates[21-23] have provided a means by which the photopic and the scotopic process can clearly be separated from each other. It is probable that the processes revealed by this method represent physiological events in the intermediate zone rather than at the receptor- or the cortical level.[20][24-25]

It has been believed that the cones have nothing to do with achromatic twilight vision,[4][26-28] but the present investigation has revealed that in the intermediate zone there occurs another kind of scotopic process having some characteristics of cone-processes, besides the so-called rod-process below the color-threshold. It is the object of the present paper to identify this newly discovered scotopic process and to elucidate its physiological significance.

Experimental

Method

The method consisted in measuring the electrical sensitivity of the eye after exposure to a brief illumination. A preliminary dark adaptation of about 40 minutes was allowed before making any electrical and photic stimulation. The electrical stimulus used was a single constant current pulse of 100 msec. in duration. The current was applied through a pair of silver electrodes placed slightly above the eyebrow and on the homolateral temple. Thus, the threshold voltage was determined to produce the least perceptible electrical phosphene.

The effect of an illumination was expressed as a percentage increase of the electrical excitability over the resting level and denoted by ζ.

Retinal areas 20° and 50° from the center of the fovea were exposed to a circular patch of 2° in visual angle illuminated by spectral light, and at different times after removal of the light stimulus the electrical excitability was determined to construct a ζ-time curve. The duration of pre-illumination was made 0.5 seconds for the reasons stated in a preceding paper.[23] For further details of experimental procedures previous papers[24)29)] should be consulted.

The intensities of spectral lights used for pre-illumination ranged between the light- and color-threshold. Thresholds for photic stimuli were determined by the method of limits: The light was diminished in intensity until it was not seen, and, in alternating runs, was increased until it was seen. The average of ten such measurements was taken as the threshold value. In such measurements the duration of a single flash was made 0.5 seconds.

The color sensation felt by the subject at the color-threshold was either yellow or blue according to the wave-lengths of spectral lights. It was found difficult to perceive any definite coloration near 505 mμ.

Accuracy of measurements

Fluctuation in the excitablity of the resting eye can be a cause of errors. Daily variations of the resting threshold voltage in our experiments were found to lie between 0.8 and 1.6 volts. The resting threshold had to be measured almost each time, and when it was found different more than 10% before and after a measurement, the latter was discarded. When fluctuations became too remarkable for some reasons, for example, due to fatigue, measurements were stopped at once. We used to determine from 5 to 10 points in a session, and a series of experiments was completed in a few sessions. The reproducibility of ζ-values was, however, so satisfactory in well-trained subjects that points determined in different sessions yielded a smooth curve.

An example is shown in Table I in which ζ-values at 1, 1.5 and 2 seconds were determined in 4 sessions. The light stimulus used was red light of 650 mμ whose intensity was adjusted each time to the color-threshold. As can be seen in this table, the standard deviations are sufficiently small.

TABLE I

Experiment Showing the Degree of Accuracy of Measurements

Pre-illumination: red right (650 mμ) at color-threshold.

Time after illumination \ Sessions	ζ-Values I	II	III	IV	Mean and standard deviation
1″	7 6 6	6 6	5.5 6.5 7.5	7 6	6.35 ±0.198
1.5″	8 7.5 7	8.5 8	8 8.5 7.5	8.5 8	7.95 ±0.165
2″	4.5 4 4.5	5 4.5	4.5 4.5 4.5	4 5	4.5 ±0.167

To raise the accuracy of measurements, various points described in a Motokawa's paper[29] should be taken into account.

Results

The time course of any ζ-time curve depends on the wave-length of pre-illuminating light, but scarcely on its intensity.[24] As the intensity of light is raised, the ζ-time curve increases in height, but remains unaltered with respect to its crest time. However, once the intensity is decreased till the light-threshold, the form of the ζ-time curves for various spectral lights becomes nearly identical, as shown in the left column of Fig. 1. The curves illustrated in this column were obtained with red (650 mμ), yellow (585 mμ), green (530 mμ) and blue (470 mμ) lights at 20° from the center of the fovea, the intensities of these light stimuli just corresponding to the light-threshold.

We can distinguish three elevations denoted by Y, B and ROD in the curves for red and blue lights, while the B elevation is less distinct in the curves for yellow and green lights. The elevation having its maximum at 4 seconds must represent the rod-process described by Motokawa *et al.*[21-22], because its crest time is 4.5 seconds measured from the onset of the light stimulus.

It has long been believed that the colorless sensation at the light-threshold is mediated by rods alone.[4][26-28] Nevertheless, it has been revealed that besides the rod-process some other elevations like Y and B

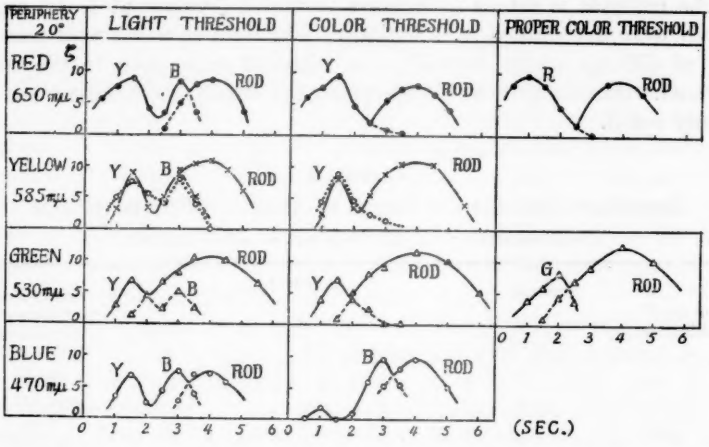

Fig. 1. ζ-time curves obtained at 20° from fovea at three intensity levels; i.e. light-, color- and proper color- threshold. Ordinates: percentage increases of electrical excitability of the human eye above resting level (ζ). Abscissas: time in sec. after termination of pre-illuminating light. The duration of pre-illumination was 0.5 sec. except for dotted curve.

appear in the curves obtained at the light-threshold. This was indeed beyond our expectation that only rod-processes would appear under this experimental condition.

In the curve for green light we encountered double thresholds when stimulating voltages were graded in sufficiently small steps. This was due to overlapping of the two processes, the rod-process on one hand, Y or B on the other.

The same is the case with the curve for yellow light. In order to make certain that the double thresholds were really caused by such overlapping, measurements were carried out under the experimental conditions under which no rod-process appeared: According to Motokawa *et al.*[21-22] no rod-process manifests itself when the pre-illumination is longer than 4 seconds. The dotted curve was obtained, using yellow light of 4 seconds and of intensity just corresponding to the light-threshold for pre-illumination. The curve shows distinct maxima at 1.5 and 3 seconds, but the rod-process can be seen no more.

According to the analysis by Motokawa[24], the ζ-time curves for red, yellow, green and blue receptors show a maximum at 1, 1.5, 2 and 3 seconds respectively. If the result of Motokawa's analysis is applicable to the data obtained with such low intensities of pre-illumination in our experiments, then it may be said that the maxima at 1.5 and 3 seconds

in our curves are to be ascribed to the yellow and the blue receptor respectively. Hence they are denoted by Y and B. Another aspect to be mentioned is that the magnitudes of the Y and B processes are nearly equal to each other in all curves.

Quite similar curves to those illustrated above were obtained at 50° from the foveal center. The intensity of pre-illumination was slightly above the light-threshold, the other experimental conditions being the same as above. They are illustrated in Fig. 2. In the set of curves the three elevations are found more conspicuous than in the curves at 20° illustrated in Fig. 1. Such clearer separation of the three processes at 50° has been caused by the circumstance that the rod-process is lower at 50° than at 20°. This finding fits in with the known properties of rods that their population density is smaller at 50° than at 20°.[30] On the other hand, the magnitudes of the Y and B processes at 50° are almost the same as at 20°. This finding may correspond to the known fact that the population density of cones at 50° is nearly the same as at 20°.[30]

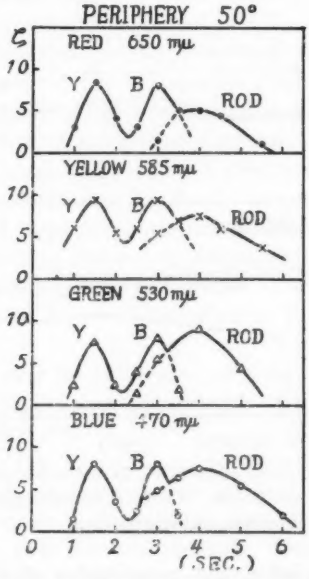

Fig. 2. ζ-time curves at 50° from fovea; other notations the same as in Fig. 1.

The curves show that the magnitudes of the three processes, Y, B and ROD depend little on the wave-lengths of spectral lights. This relation can be seen more clearly in Fig. 3A, in which the magnitudes

of the three processes are plotted as ordinates against the wave-lengths as abscissas. It is obvious from this figure that the magnitudes of the Y and B processes are equal to each other and remain constant throughout the entire range of spectral wave-lengths.

It was expected that the rod-response would remain constant over the entire range of wave-lengths at the light-threshold. In reality, however, the rod-response was found a little greater over a middle range than at longer and shorter wave-length ends of the spectrum. The reasons are unknown at present, but a tentative explanation for this situation may be as follows: In our measurements photic stimulation was repeated at an interval of about 10 seconds, so that some cumulative effect might have caused such enhancement observed over the middle range of the spectrum as would be obtained with over-threshold spectral lights.[22]

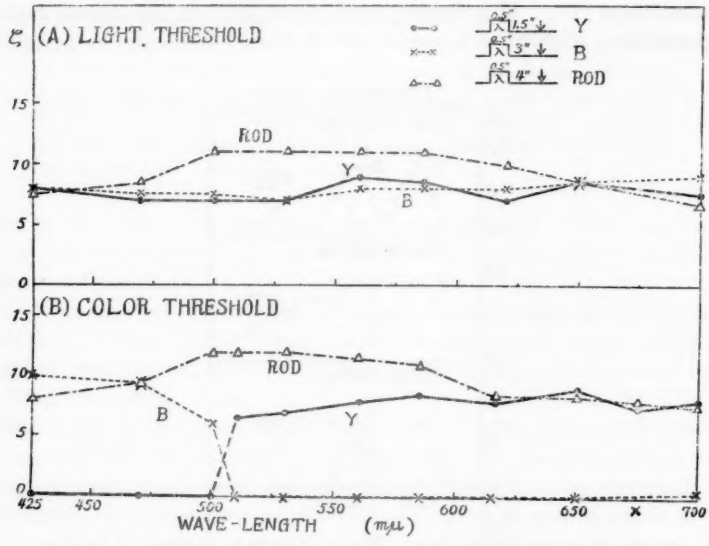

Fig. 3. Spectral distributions of Y-, B- and rod-processes. Procedure of experimentation is shown in inset, in which λ indicates spectral light of various wave-lengths, and arrows electrical stimulation.

As will be shown later, the magnitudes of the Y and B processes change but little and remain equal to each other when the intensity is raised above the light-threshold. In this manner, both processes appear always in pairs unless the intensity of light surpasses the color-threshold, and may be regarded as a unit process. I propose to call it "a twin-process" for the sake of simplicity.

Another series of experiments was carried out at the color-threshold. The results are shown in the middle column of Fig. 1. The ζ-time curves generally consist of two elevations which can be identified with the Y- and the rod-process for red, yellow and green lights and with the B- and the rod-process for blue light. It is to be noted that either of the two components of the twin-process is depressed at the color-threshold.

This relation is seen more clearly in the spectral distributions of the Y-, B- and rod-processes determined at the color-threshold in Fig. 3B. As can be seen in this figure either component Y or B of the twin-process is depressed according to whether the wave-length of pre-illuminating light is shorter or longer than 505 mμ. This finding just corresponds to the psychological fact that at the color-threshold of the peripheral retina, spectral lights of longer wave-lengths give rise to a yellow sensation, while those of shorter wave-lengths elicit a blue sensation.[31-33] At 505 mμ it was found difficult to determine the color-threshold because of a high degree of desaturation.

The rod-response showed a flat rise in the mid-spectrum similar to that observed at the light-threshold.

Next, the dependence of the magnitudes of the twin-process and rod-process on the intensity of pre-illuminating light was investigated. In Fig. 4 the magnitudes are plotted as ordinates against the logarithms of the intensities in physiological units as abscissas. Between the light- and color-threshold these magnitudes remain constant irrespective of the intensity. Above the color-threshold the Y and the rod-process increase as the intensity of red light rises, whereas the B component of the twin-process is out of sight (A), and the Y component is in turn depressed in the case of blue pre-illuminating light (B). It seems that the all-or-none law approximately holds for the depression of the Y or B component of the twin-process.

It is to be noted that the depression of either component of the twin-process is the only change that occurs with the development of a color sensation, blue or yellow.

As can be seen in Fig. 4, the Y and B components of the twin-process are equal in magnitude in the colorless interval and are complementary to each other. Therefore it is probable that the twin-process subserves colorless sensations as does the rod-process. They must co-operate with each other in producing colorless sensations below the color-threshold. Thus the present experiment has provided evidence that there are two kinds of scotopic mechanisms in the human retina.

In the right column of Fig. 1 two ζ-time curves are illustrated, which were obtained for red and green lights of intensities high enough to elicit specific color sensations of red and green (the proper color-thrshold).

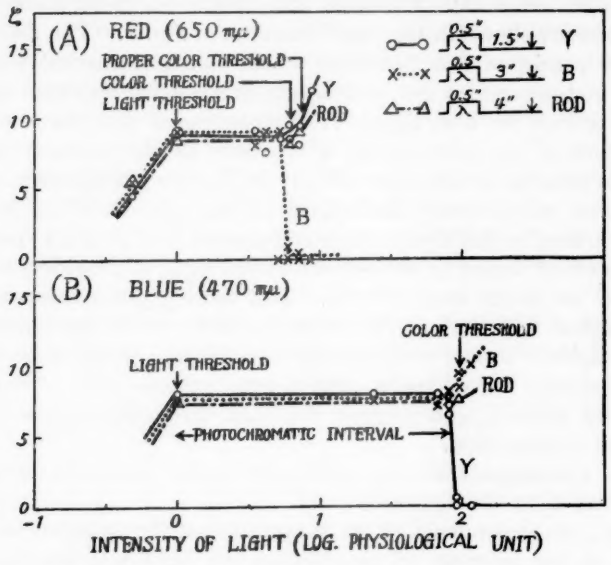

Fig. 4. Relation between magnitudes of Y-, B- and rod-processes and logarithm of light intensity. Procedure of experimentation is shown in inset.

The crest time of the preceding elevation of the curve for red light is now 1 second instead of 1.5 seconds, while that of the preceding elevation of the curve for green light is 2 seconds. Since these values of crest time are characteristics of the red and green receptors respectively, this finding corresponds well with the sensory fact that at these intensities the specific sensations of red and green were evoked.

Discussion

It has long been taken for granted that the light-threshold is determined by the excitation of rods alone.[4)26-28)]

The present experiment has, however, shown that besides the so-called rod-process, the twin-process participates in achromatic twilight vision.

The question now arises as to whether the two kinds of scotopic processes distinguished by our method represent the two kinds of rods which were presupposed by some workers.[34-37)] There is, however, no histological evidence that in the human retina there exist two kinds of rods.[17)]

It is certain that our so-called rod-process has all characteristics of rods, for example, 1. the spectral distribution of our rod-response coincides

with the scotopic visibility curve,[22] 2. the spatial distribution of our rod-response is approximately in proportion to the density distribution of rods,[30] 3. light of intensity below the color-threshold can elicit this response, 4. this response originates in on-elements of the retina[21][37] and 5. the time constant of this process is slower than that of any photopic process.[21]

Then, has our twin-process also the characteristics of rods? The properties of the twin-process are, however, quite different from those of our rod-process except for a few points. As mentioned above, the magnitudes of the twin-process at 20° from the center of the fovea are almost equal to those at 50°. This distribution is in line not so much with the density distribution of rods as with that of cones. The crest times of the twin-process measured from the end of pre-illumination are independent of the duration of pre-illumination, while the crest time of the rod-process so measured decreases as the duration of pre-illumination increases. This difference derives from the situation that pure off-elements or on/off-elements are concerned with the twin-process, while pure on-elements are responsible for the rod-process.[21][37] The twin-process is identical with the photopic processes at the fovea so far as these properties are concerned. The Y component of the twin-process has a crest time of 1.5 seconds so that it may be regarded as representing excitation of the yellow mechanism. Similarly the B component of the twin-process can be considered to represent excitation of the blue mechanism, because its crest time is 3 seconds.

From what has been said, it is apparent that the twin-process has some properties characteristic of photopic processes. On the other hand, the following properties suggest that the twin-process is a scotopic process: 1. This process appears only below the color-threshold. 2. It mediates scotopic colorless sensations together with the rod-process. 3. The magnitudes of the twin-process at the light-threshold are constant irrespective of the wave-lengths of pre-illuminating lights; in other words, a spectral sensitivity curve determined with a constant twin-process as an index is identical with a scotopic spectral sensitivity curve. 4. No twin-process appears at the fovea.[38]

From the properties mentioned above we may draw a conclusion that the twin-process is a scotopic process having some properties similar to those of photopic processes. Above all things it is to be noted that the reciprocal of light intensities of spectral lights necessary for eliciting a constant magnitude of the twin-process yields a scotopic spectral sensitivity curve (cf. Fig. 3A). It is generally believed that visual purple is responsible for the scotopic spectral sensitivity curve.[11-14] Therefore, it is conceivable that the twin-process is mediated by visual purple like the

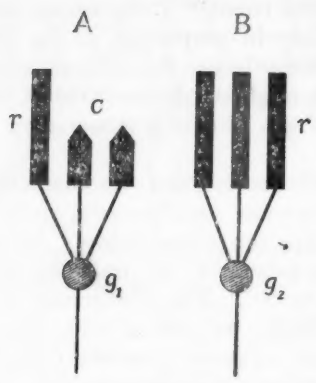

Fig. 5. A: cone-system associated with rod. B: pure rod-system. c: cones. r: rods. g_1 and g_2: bipolar cells.

rod-process.

As mentioned above, retinal processes revealed by our method represent physiological events in the intermediate zone or retinal network. Polyak provided histological evidence for convergence of cones and rods into a common bipolar cell (see A in Fig. 5). In such a system the bipolar cell would be excited by impulses initiated in the rod at the light-threshold, because the visual purple contained in the rod may be considered more sensitive to light than any cone-substance.[39] If the excitation process of this bipolar is to correspond to the type of photopic processes, such a system must exhibit dual behavior similar to that of the twin-process; the spectral sensitivity of such a system will be determined by visual purple, while the time constant of the excitation process will correspond to that of cone-processes.

From this consideration it is very likely that the twin-process represents the excitation of an intraretinal system receiving impulses both from cones and rods (A in Fig. 5).

On the contrary, the rod-process may be considered to represent the excitation of an intraretinal system receiving impulses from rods alone (B in Fig. 5).

It has been shown above that the depression of either component of the twin-process is associated with development of a color sensation when the intensity is raised up to the color-threshold. Let us suppose a system such as represented by A in Fig. 5 to be exposed to colored light of intensity above the color-threshold. The bipolar g_1 will now receive impulses not only from the rod, but also from the cones, because the intensity of light is sufficient to excite the cones as well.

Since it is at the color-threshold or above it that one component of the twin-process drops out, the impulses from the cone must play some role in this phenomenon; in other words, inhibitory impulses started at the cone convert the colorless twin-process into a yellow or a blue process according to the wave-length of the light activating the cone in question. In this way a color process is released by inhibition. Needless to say, the color process so released will further be strengthened by active excitation, and other color processes will also be activated when the intensity of light is raised further.

The important part played by retinal inhibition in the formation of color sensations has been discussed by previous workers,[40-42] and there are some physiological evidences for inhibitory processes in the retina.[43-49]

Summary

Retinal processes were studied by the method of electrostimulation at 20° and 50° from the fovea.

1. At the light-threshold there appear three processes of different time courses. The slowest one represents the excitation of rods. The other two processes correspond to the yellow and the blue process respectively, judging from their crest times. Therefore, they are denoted by Y and B.

2. At the light-threshold and in the photochromatic interval, the two processes, Y and B appearing always hand in hand, are equal to each other in magnitude and remain constant irrespective of the wave-lengths of illuminating lights. Therefore, they are called " a twin-process." This process subserves scotopic colorless sensations in conjunction with the rod-process.

3. At the color-threshold, either Y or B component of the twin-process is depressed according to whether the wave-length of illuminating light is shorter or longer than 505 mμ, but the other component remains intact. This finding corresponds to the psychological fact that at the color-threshold spectral lights give rise to yellow or blue sensation.

4. The twin-process is a scotopic process having some properties similar to those of photopic processes. It differs from the rod-process in the following points; i) it originates in off-elements or on/off-elements, ii) it exists only below the color-threshold, iii) its spatial distribution corresponds to the density distribution of cones, iv) its time constants are much shorter than that of the rod-process.

5. The important role played by inhibition in the formation of color sensations is discussed.

I am greatly indebted to Prof. K. Motokawa for his many valuable dis-

cussions and kind guidance.

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Newborn Virus Pneumonitis (Type Sendai) III. Pathological Study

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This is to report on the 9 autopsy cases clinically observed by Sano and his co-workers (See page 56). In all cases hemorrhagic pneumonia was observed in both sides and in all lobes of the lung, showing the appearance of so-called splenization. These changes were more conspicuous in cases with a short clinical lapse. In thoracal cavity there were no accumulation of fluid nor fibrinous precipitates. Bleeding was found in the serosa of bodily cavities, in the mucosa of alimentary canals and in the retroperitoneum etc. The leptomeninx was congested and slightly turbid, in 4 cases the spleens were slightly enlarged and in 7, we observed hemorrhagic erosion in the stomachs.

Histological examination: In the affected part of the lung the alveolar septa were often greatly distended owing to excessive blood congestion and cellular infiltration, giving the appearance of interalveolitis. The infiltrating cells mainly consisted of medium-sized mononuclear cells and cells with oblong nuclei, mingled with a small number of leucocytes. Edema, atelectasis and emphysema were found scattered in disorder among the areas of hemorrhages and interalveolitis. In some part desquamation of the bronchial epithelium was visible, but very little, if any, cell infiltration of the wall. No hyaline membrane was found on the surface of alveoli and bronchioli, nor any hyaline thrombus in the capillaries. Fibrin and swallowed epithelium were occasionally found in the air sacs. Inspite of hard investigation, no inclusion bodies could be found in the bronchial- and alveolarepithelium. Beside the above, serous hepatitis, light leptomeningitis and occasionally nephrosis were observed.

In the mice inoculated intranasally with the materials obtained from 5 autopsy cases evident septum-pneumonia with mononuclear cell infiltration and hemorrhages were found, quite similar to those above noted. Spleen, liver and kidney were also affected. No marked changes were seen in the brain and the heart. The same effect was apparent on the lungs of mice inoculated intraperitoneally or intracerebrally with the virus. (See page 62)

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Studies on Enema

I. Influences of the pH Value of Enema on the Absorption of Calcium in the Large Intestine

By

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Introduction

As regards the correlationships between the absorption of calcium and pH value, Telfer[1] claimed that absorption occurs in the upper part of small intestine where the reaction is relatively on the acid side. Hesse and Barndt[2] reported that the absorption of calcium is related to the pH of gastro-intestinal tract, and that there is no marked difference in the absorption between dissolved or dissociated Ca-salts and insoluble Ca-salts, consequently any Ca-salt is absorbed in a same manner. Klinke[3] stated that the absorption of calcium is influenced by the solubility of Ca-salt and the hydrogen ion concentration of the solution. Irving[4] reported that, when calcium chloride acidified with acetic acid is introduced into the duodenum of dog, remarkably better absorption is observed compared with the case of the introduction of calcium chloride alone. Vogt[5] stated that, as regards the absorption of inorganic salts in the intestinal tract, active actions in addition to pure physical actions (osmotic pressure or filtration) of the intestinal tract influence the absorption of inorganic salts, and that bile accelerates the absorption of inorganic substances. Klinke[6] also reported that both bile and biliary acid possess dissolving action against calcium phosphate and calcium carbonate, and especially bile has a remarkable dissolving action against calcium carbonate.

In our Department, Yoshimoto,[7] Usui[8][9], Hitomoto[10][11][12] and Kato[13][14] have thoroughly investigated the absorption of calcium in the large intestine and the influences of bile or biliary acid on the absorption of calcium to confirm that the absorption of calcium preparations, especially of calcium chloride, in the large intestine is remarkably accelerated in the presence of bile constituents, especially of biliary acid, of various animals, and that the permeability of large intestine, especially of colon

descendens, to calcium is extremely enhanced, and simultaneously that, in the presence of calcium preparation, the absorption of biliary acid is accelerated. On that occasion, it was also learnt that, within the range of pH value of the enema employed in the experiments by Hitomoto, no particular influences of the change in pH are exercised on the absorption of calcium in the large intestine.

Reviewing the above, the author actively changed the pH of the enema of calcium preparations and investigated as to how the absorption of calcium in the large intestine is influenced by it. The same influences in the cases of oral administration of calcium preparations and of the mixed enema of calcium preparation and ox bile of varying pH are also investigated simultaneously.

Experimental

Materials and Methods

Mature rabbits weighing approximately 2 kg. were employed. Experiments were started when they were hungry and no food was fed during the experiments.

Samples of rabbit serum were prepared from the blood obtained by heart puncture. The determination of serum calcium was performed by the modified Kramer-Tisdall method with 1 cc. of serum each time.

The enema was administered generally following the method described by Yoshimoto, Usui, Hitomoto and Kato in their previous papers.

Calcium preparations used for the experiments were calcium chloride and calcium sulfate. They were used in the form of solution or suspension of requisite concentrations.

In the experiments with calcium preparations in combination with animal bile, ox bile was adopted. It was prepared to be 1 cc. of ox bile equivalent to 1 g. of fresh bile.

For the adjustment of pH of enema solution or preparation for oral administration, caustic soda, acetic acid, lactic acid or hydrochloric acid was used. The pH values were determined by "Toyo Roshi" test papers.

Results

I. Experiments with the application as enema

Cases where enema solution was used which had been adjusted to various pHs with 0.1 *N NaOH*

After 5% calcium chloride solution was adjusted at pH 7.0, its 10 cc. per kg. was administered as enema. After 15 minutes, a slight increase of calcium in the serum was observed. However, a similar increase was

observed in the case of the preparation without adjustment of pH.

When the pH of the same preparation was adjusted to pH 8.0 and administered in the same manner, the serum calcium content demonstrated a definite increase. It reached from 14.62 to 26.71 mg/dl after 75 minutes, and it was maintained at 25.44 mg/dl even after 210 minutes. With distilled water adjusted at pH 8.0, no increase in the serum calcium was observed, and even the serum calcium showed a tendency of decrease as time passed.

When the pH of the same preparation was adjusted at pH 9.0 and administered in the same manner, no remarkable change in serum calcium content was noted. Only very slight increase was noticed after 15 minutes (Table I).

TABLE I

Experiments with Enema Solution Whose pH was Adjusted with 0.1 *N* NaOH

Rabbit No. sex	Weight (kg.)	Room temperature (°C)	Substances administered and dosage	Method of administration and pH	Time (min.)	Serum calcium content (mg/dl)	
No. 31 ♀	2.100	24.0	5% Calcium chloride 10 cc. per kg.	E. 7.0	N	14.41	14.20
					15	18.02	15.05
					75	14.41	13.78
No. 32 ♂	2.000				210	13.14	12.92
					24h	12.92	12.50
No. 33 ♂	2.200	25.0	Distilled water 10 cc. per kg.	E. 8.0	N	13.14	
					15	12.92	
					75	12.29	
					210	12.29	
					24h	11.87	
No. 34 ♂	1.900	25.0	5% Calcium chloride 10 cc. per kg.	E. 8.0	N	14.62	13.78
					15	17.59	20.77
					75	26.71	17.38
No. 35 ♀	2.500	24.0			210	25.44	13.78
					24h	14.62	13.14
No. 36 ♀	2.100	24.5	5% Calcium chloride 10 cc. per kg.	E. 9.0	N	13.99	13.99
					15	17.59	15.05
					75	13.99	13.99
No. 37 ♀	2.200				210	13.56	13.99
					24h	12.72	12.92

E. = Enema.

Cases where enema solution was used which had been adjusted to various pHs with 10% *acetic acid*

When 5% calcium chloride solution was adjusted to pH 5.0 and its 10 cc. per kg. was administered as enema, no remarkable changes in the serum calcium content was noted. Similarly, when the pH was adjusted

to pH 4.0, no evident changes in serum calcium content was recorded.

When the same solution was adjusted to pH 3.0, the serum calcium content was found remarkable increased. In 2 cases of rabbit, from 13.78 to 23.53 mg/dl and from 13.14 to 28.83 mg/dl respectively after 15 minutes, and 16.53 mg/dl, 21.20 mg/dl respectively after 75 minutes were recorded. Their normal values were recovered after 24 hours. With distilled water adjusted at pH 3.0, no increase in serum calcium content was noted.

When the pH of 5% calcium chloride solution was adjusted to pH 2.8, similarly to the case of pH 3.0, the serum calcium content was found increased. In 2 cases of rabbit, the content was recorded as 12.50–21.20 mg/dl and 11.02 –20.35 mg/dl respectively after 15 minutes, and it decreased gradually to recover their normal values after 210 minutes.

With 5% calcium sulfate solution adjusted at pH 2.8, the serum calcium content was found increasing as time passed, and in 2 cases of rabbit, it reached 11.66–24.38 mg/dl and 12.92–24.16 mg/dl respectively after 210 minutes. However, the velocity of absorption was slower compared with that of calcium chloride.

When 10 cc. per kg. of 5% calcium sulfate and 0.5 g. of ox bile was administered as enema in combination (pH 3.0), an increase of 5 mg/dl was noted in 15 minutes. Approximately the same value was maintained even after 75 minutes, and began decreasing after 210 minutes.

In the case of enema with the combination of 5% calcium sulfate and 1 g. of ox bile (pH 2.8), increase of 5.31 mg/dl and 7.37 mg/dl respectively in 15 minutes was recorded, and both cases became fatal in 75 minutes. The serum calcium content at the time of death was 17.38 mg/dl and 17.80 mg/dl respectively. This death was considered to be due to abnormal absorption of biliary acid contained in the bile occurred simultaneously with the absorption of calcium (Table II).

Cases where enema solution was used which had been adjusted to pH 2.8 *with* 10% *lactic acid*

When 10 cc. per kg. of 5% calcium chloride solution adjusted to pH 2.8 with 10% lactic acid administered as enema, the serum calcium content evidently demonstrated an increase. In 2 cases of rabbit, 14.84-20.14 mg/dl and 13.99–20.35 mg/dl respectively was recorded in 15 minutes, and approximately their normal values were recovered after 75 minutes. With distilled water adjusted at pH 2.8, no remarkable changes in the serum calcium content were noted.

With 5% calcium sulfate solution adjusted at pH 2.8, only slight increase in serum calcium content was noticed.

In the case with the combination of 5% calcium sulfate and 0.5 g. of ox bile, an increase of 5 mg/dl in 15 minutes was observed showing an

TABLE II

Experiments with Enema Solutions Whose pH was Adjusted with 10% Acetic Acid

Rabbit No. Sex	Weight (kg.)	Room temperature (°C)	Substances administered and dosage	Method of administration and pH	Time (min.)	Serum calcium content (mg/dl)	
No. 38 ♀	2.500	23.5	5% Calcium chloride 10 cc. per kg.	E. 5.0	N	13.99	13.56
					15	13.56	13.14
					75	13.35	13.14
No. 39 ♂	2.400				210	12.29	12.08
					24h	12.29	12.08
No. 40 ♂	2.100	21.0	5% Calcium chloride 10 cc. per kg.	E. 4.0	N	13.99	12.29
					15	14.84	11.44
					75	14.62	10.81
No. 41 ♀	2.500				210	13.56	10.81
					24h	12.29	11.66
No. 42 ♀	2.200	21.0	5% Calcium chloride 10 cc. per kg.	E. 3.0	N	13.78	13.14
					15	23.53	28.83
					75	16.53	21.20
No. 43 ♂	2.100				210	15.90	15.90
					24h	13.14	13.14
No. 44 ♀	1.900	21.0	5% Calcium chloride 10 cc. per kg.	E. 2.8	N	12.50	11.02
					15	21.20	20.35
					75	16.96	16.96
No. 45 ♀	1.900				210	13.14	12.29
					24h	11.66	12.08
No. 46 ♀	2.100	24.5	Distilled water 10 cc. per kg.	E. 2.8	N	14.80	
					15	14.62	
					75	13.35	
					210	13.35	
					24h	12.72	
No. 47 ♂	2.400	24.5	Distilled water 10 cc. per kg.	E. 3.0	N	13.14	
					15	13.35	
					75	11.87	
					210	10.60	
					24h	10.60	
No. 48 ♂	2.400	24.0	5% Calcium sulfate 10 cc. per kg.	E. 2.8	N	11.66	12.92
					15	15.26	18.65
					75	19.50	20.35
No. 49 ♂	2.100	24.5			210	24.38	24.16
					24h	12.72	Died
No. 50 ♂	2.400	26.5	5% Calcium sulfate 10 cc. per kg. Ox bile 0.5g. per kg.	E. 3.0	N	11.66	11.66
					15	16.74	16.74
					75	16.11	16.53
No. 51 ♂	2.400				210	14.41	12.92
					24h	11.66	11.66
No. 52 ♀	2.000	24.0	5% Calcium sulfate 10 cc. per kg. Ox bile 1 g. per kg.	E. 2.8	N	12.92	12.92
					15	18.23	19.29
						75m.Died	75 m. Died
No. 53 ♂	2.000					17.38	17.80

acceleration of absorption of calcium in the large intestine though slightly.

Cases where enema solution was used which had been adjusted to pH 2.8 *with* 0.1 *N hydrochloric acid*

When 10 cc. per kg. of 5% calcium chloride solution adjusted to pH 2.8 was administered as enema, the serum calcium content was found remarkably increased in 15 minutes. In 2 cases of rabbit, 14.20–29.89 mg/dl and 14.20–21.20 mg/dl respectively was recorded after 15 minutes, and both of the cases became fatal after 75 minutes and 210 minutes respectively. At the time of death, the serum calcium content was 26.71 mg/dl and 28.19 mg/dl respectively. Approximately 10 cc. of colourless transparent peritoneal fluid was obtained from Rabbit No. 65. The calcium content of this sample of peritoneal fluid was as high as 32.22 mg/dl. The control with distilled water did not demonstrate any remarkable change in the calcium content of serum.

II. Experiments with oral administrations

Cases with solutions without pH adjustment

When 20 cc. per kg. of 5% calcium chloride solution was administered orally, a slight increase in serum calcium content was noted after 15 minutes and 75 minutes, but approximately normal value was recovered after 210 minutes. With 10 cc. per kg. of the same solution administered orally, also a slight increase in serum calcium content was noted, but the amount increased was found further smaller.

With 20 cc. of the same solution combined with 1 g. of ox bile per kg. administered orally, a marked increase in serum calcium content was noticed. In 2 cases of rabbit, the content increased from 13.56 mg/dl to 21.20 mg/dl and from 14.68 mg/dl to 26.78 mg/dl in 15 minutes respectively, and 20.14 mg/dl and 21.38 mg/dl after 75 minutes. Even after 210 minutes, the increment, though slight, was maintained above normal.

With 10 cc. of the same solution combined with 1 g. of ox bile per kg. administered orally, also a remarkable increase in serum calcium content was observed. In 2 cases of rabbit, it increased from 17.72 mg/dl to 21.16 mg/dl and from 16.63 mg/dl to 22.89 mg/dl in 15 minutes, and their approximate normal values were recovered after 210 minutes (Table III).

Cases where solution was used which had been adjusted to pH 2.8 *with* 10% *acetic acid*

Oral administration of 10 cc. per kg. of 5% calcium chloride with adjusted pH 2.8 induced the increase in the serum calcium content in slight degree. However, the value was not much different from that of control cases. Even with 20 cc. per kg. of the same solution, no marked change in the serum calcium content was noticed similarly to the control cases.

TABLE III

Experiments with Solutions without pH Adjustment

Rabbit No. Sex	Weight (kg.)	Room temperature (°C.)	Substances administered and dosage	Method of administration and pH	Time (min.)	Serum calcium content (mg/dl)	
No. 85 ♀	1.700	26.0	5% Calcium chloride 20 cc. per kg.	O.A. 6.0	N	14.68	14.68
					15	17.94	19.00
					75	17.28	19.00
No. 86 ♂	1.700				210	15.55	16.20
					24h	13.82	14.08
No. 87 ♀	2.300	25.0	5% Calcium chloride 10 cc. per kg.	O.A. 6.1	N	11.02	12.72
					15	12.50	13.99
					75	12.72	13.99
No. 88 ♀	2.400				210	11.87	12.50
					24h	10.60	11.66
No. 89 ♀	1.900	24.5	5% Calcium chloride 20 cc. per kg. Ox bile 1 g. per kg.	O.A. 6.3	N	13.56	14.68
					15	21.20	26.78
					75	20.14	21.38
No. 90 ♂	1.700				210	14.62	17.28
					24h	13.14	14.68
No. 91 ♀	1.800	27.0	5% Calcium chloride 10 cc. per kg. Ox bile 1 g. per kg.	O.A. 6.3	N	17.72	16.63
					15	21.16	22.89
					75	18.58	20.08
No. 92 ♀	1.900				210	17.50	16.63
					24h	15.55	14.84

O.A.....Oral administration

With 20 cc. of the same solution combined with 1 g. of ox bile per kg. administered orally, the serum calcium content was found markedly increased. In both of the 2 cases, the content increased from 14.68 mg/dl to 21.41 mg/dl and from 12.29 mg/dl to 25.44 mg/dl respectively in 15 minutes, and it was 23.74 mg/dl and 25.01 mg/dl after 75 minutes, comparing with which no marked difference was noticed between the control tests.

Cases where solution was used which had been adjusted to pH 2.8 *with* 10% *lactic acid*

When 20 cc. per kg. of 5% solution of calcium chloride adjusted to pH 2.8 was orally administered, a slight increase in serum calcium content was noted after 15 and 75 minutes, but no marked difference was observed compared with the values obtained in the control cases. No difference was noticed with 10 cc. per kg. of the same solution.

With combined administration of 20 cc. per kg. of the same solution and 1 g. of ox bile per kg., increase in serum calcium content was noted. In 2 cases, an increase from 12.92 mg/dl to 22.04 mg/dl and 12.08 mg/dl to 20.14 mg/dl respectively was demonstrated. Comparing with the

values obtained in the control cases, the values did not show any remarkable difference.

Cases where solution was used which had been adjusted to pH 2.8 *with* 0.1 *N* hydrochloric acid

When 20 cc. or 10 cc. per kg. of 5% calcium chloride solution adjusted to pH 2.8 was administered orally, the increase in serum calcium content was generally slight similarly to the control cases. However, in the cases with 20 cc. per kg., evident increase was occasionally observed.

With 20 cc. of the same solution combined with 1 g. of ox bile per kg., the content was found evidently increased, showing, in 2 cases, from 12.52 mg/dl to 19.50 mg/dl and from 14.25 mg/dl to 20.08 mg/dl respectively in 15 minutes, and 21.20 mg/dl and 19.00 mg/dl after 75 minutes. However, comparing with the values obtained in the control cases, the above values did not show any remarkable difference.

Cases with calcium sulfate solution without pH adjustment

When 10 cc. per kg. of 5% calcium sulfate solution was administered orally, a slight increase in serum calcium content was noted after 15 minutes and 75 minutes.

With 10 cc. of the same solution combined with 1 g. of ox bile per kg., only a slight increase in serum calcium content was noted similarly to the above.

Cases with calcium chloride solution applied after the ligature of gastric pylorus

Rabbit was fixed in dorsal position, and a longitudinal incision on the median line, approximately 5 cm. in length, from the xiphoid process was given. Then, the pylorus was drawn out of the incision by a finger inserted along the gastric fundus. The transitional portion of the pylorus toward the duodenum was then bound tight with No. 3 suture silk thread. The pylorus was then reinstated in the peritoneal cavity, and the peritoneum and skin were sutured. After the above operation was completed, the solutions were administered orally as prescribed.

When 10 cc. per kg. of 5% calcium chloride alone, or combined with 1 g. per kg. of ox bile was administered orally, absolutely no increase in serum calcium content was observed.

Summary

By actively changing the pH of the enema solution of calcium preparations, especially of calcium chloride, the influences of the varying pH of the enema solution on the absorption of calcium in the large intentine was investigated in the first place.

When the reaction of the enema was shifted to the alkaline side with NaOH, the absorption of calcium chloride in the large intestine was evidently enhanced at pH 8.0. At pH 7.0 or pH 9.0, the absorption

remained the same as in the control tests with the solution without adjustment of pH, and there was no enhancement of absorption noted. When the reaction of the enema was shifted to the acid side with acetic acid, lactic acid or hydrochloric acid, the absorption of calcium chloride in the large intestine was remarkably enhanced at pH 2.8 in all cases. Especially, when the reaction was adjusted with hydrochloric acid, the absorption was most distinctly enhanced, and all the rabbits used demonstrated intoxication symptoms and became fatal. As already reported by Hitomoto and Kato, the calcium content in the peritoneal fluid in such cases was found extremely increased.

Previously, Kato reported a very interesting result that when calcium preparations combined with the mixture of glycocoll and glucose is administered as enema, the absorption of calcium chloride in the large intestine is greatly enhanced, and further, that calcium lactate and calcium sulfate, which are usually not absorbed from the large intestine, are also absorbed. Whereas, I confirmed that, when calcium sulfate solution is acidified to pH 2.8 with acetic acid, calcium sulfate is absorbed in the large intestine, though slower compared with calcium chloride, and the serum calcium content is somewhere about 24 mg/dl even after 210 minutes. Adjustment of the reaction to pH 2.8–3.0 combined with ox bile does not particularly enhance the absorption compared with the above results, but when too much ox bile is combined, intoxication death caused by abnormal absorption of biliary acid and excess of calcium content in the serum is observed.

In the case of oral administration, even doubled amount of calcium chloride solution of the case of enema (20 cc. per kg. of 5% calcium chloride solution) generally increase the serum calcium content only slightly. Whereas, when ox bile is combined, the serum calcium content increases rapidly indicating the enhanced absorption of calcium in the small intestine. Differing from the case of enema, in the case of oral application, no particular enhancement of the absorption of calcium is observed even the reaction of calcium chloride solution is adjusted to pH 2.8 with acetic acid, lactic acid or hydrochloric acid. Further, when ox bile is combined with calcium chloride solution with adjusted pH, no particular difference is noted in the influence of bile from that in the case combined with the same solution without pH adjustment. Despite the fact that the absorption of calcium in the small intestine does not demonstrate any difference between that of calcium solution with adjusted pH or without pH adjustment combined with ox bile, the absorption of calcium administered in combination with ox bile induces much more rapid and distinct enhancement of calcium absorption compared with that of the application of calcium alone. Consequently, it became essential to know calcium

absorption in the stomach. When calcium chloride solution was orally administered after the pylorus of stomach was ligatured, the fact, that the serum calcium content did not increase during the elapse of 210 minutes from the administration even in the combined application with ox bile, was confirmed. By the above fact, it is presumed that the rapid increase in serum calcium content in the case of combined application with ox bile may be induced by rapid transfer of calcium chloride solution from the stomach to the small intestine and enhancement of calcium absorption in the small intestine by ox bile.

Conclusions

1. When 5% calcium chloride solution adjusted to pH 8.0 with 0.1 *N* NaOH is administered as enema, the serum calcium content increases and calcium absorption in the large intestine is enhanced.

2. Similarly to the above, the absorption of calcium in the large intestine is enhanced when the same solution is administered as enema after pH adjustment to pH 3.0 or pH 2.8 with acetic acid, lactic acid or hydrochloric acid. Most remarkable enhancement of calcium absorption is noted when the pH of the solution is adjusted with hydrochloric acid.

3. When the pH is adjusted to pH 2.8 with acetic acid, calcium preparation which is generally not absorbed from the large intestine such as calcium sulfate is also absorbed from the large intestine and the serum calcium content increases. In this case, no particular influences are exercised by the combined administration with ox bile. However, intoxication death caused by abnormal absorption of biliary acid is observed.

4. In the case of oral administration of calcium chloride solution, enhancement of absorption is not evidently recognized even the reaction of the solution is shifted to pH 2.8.

5. In the case of oral administration of calcium chloride solution, calcium absorption in the small intestine is rapidly enhanced when ox bile is administered in combination.

6. The absorption of calcium chloride in the stomach is not recognized.

In short, the absorption pattern of calcium chloride in the large intestine is remarkably influenced by the pH of the enema solution. Most remarkable enhancement of absorption is observed at pH 8.0 or in the neighbourhood of pH 2.8–3.0. Contrary to this, the influence of pH is not so remarkable in the case of oral application. It is interesting to note that the absorption of calcium sulfate in the large intestine is fairly evident on the acid side of the solution.

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Studies on Enema

II. Influences of Various Narcotics on the Absorption of Calcium and Histamine in the Large Intestine

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Introduction

Hitomoto[1] has reported that the pattern of calcium absorption in the large intestine of rabbit under anesthesia follows approximately the same that under non-anesthetic condition, and that the calcium absorption in the large intestine is not enhanced by the anesthesia with urethane. On the other hand, Kondo (unpublished)[2] confirmed that, when solutions of calcium compounds combined with various narcotics, especially with chloral hydrate are administered as enema, the calcium absorption in the large intestine is remarkably enhanced, and that the calcium absorption is not influenced by magnesium sulfate. Further, Tsunoo, Sekiya and Shirado[3] have reported that, in the case when penicillin combined with urethane is administered as enema, the absorption of penicillin is distinctly enhanced and the blood level is maintained higher and longer compared to the combination with other substances (glucose, glycocoll, chloral hydrate, taurin, magnesium sulfate etc.). As stated above, the pattern of absorption of various substances in the large intestine varies as the method of administration and the substances combined vary.

When histamine is infused into alimentary canal, the pattern of absorption of histamine from various parts of the canal is not equal. According to Meakins and Harrington,[4] histamine is absorbed best from the small intestine, and its absorption from stomach or large intestine is very slow. Mellanby[5] also reported that the absorption of histamine from stomach or large intestine is generally not recognized. Investigating the absorption of histamine from intestinal canal in detail, Yamada[6][7][8] claimed that the minimum lethal dosis of histamine for rabbit when infused into duodenum is 50 mg. per kg., and that it requires 5–6 to 15–16 hours to kill rabbit. Further, Yamada also reported that, in the case of hista-

mine infusion into large intestine, he did not recognize any cases of intoxication or death even with the administration of histamine amounting to 40–50 mg. per kg.

In this instance, the author attempted the investigation on the influences of narcotics on the calcium absorption in the large intestine following the studies on the influences of pH on the absorption of calcium in the large intestine, which has been published previously. In addition, the influences of the combination of narcotics on the absorption of histamine in the large intestine in an attempt to help elucidating the mechanism of the calcium absorption in the large intestine.

Experimental

Materials and Methods

The experiments were performed following the method described in the previous paper in general.

Calcium preparations employed were calcium chloride and calcium sulfate, from which solutions or suspensions of requisite concentrations were prepared to be administered as enema.

As histamine preparation, histamine hydrochloride (Takara Seiyaku) was adopted, from which fresh solution was prepared in each time for experiment. The isolation of blood histamine was performed according to Nakamura's procedures[9] with accurately measured 10 cc. of blood obtained by heart puncture. The estimation of histamine was biologically performed using guinea pig intestine following the procedures by Yokoyama[10] and Akiyama.[11] In view of the velocity of absorption in the large intestine and the concentration in the blood known as the results of numerous studies on the enema performed in the Department in the past, bleeding was performed 30 minutes after histamine enema. In case the animal died earlier than 30 minutes from the enema, blood was collected by opening the thorax immediately after the death.

The pH of enema solution or duodenal infusion solution was determined with Toyo Roshi's test papers.

Results

On the calcium absorption under non-anesthetic condition (Table I)

When 20 cc. per kg. of 5% calcium chloride solution was administered orally, a slight increase in the serum calcium content was noted after 15–75 minutes, and approximately normal value was recovered after 210 minutes.

In the case of duodenal application of 20 cc. per kg. of 5% calcium chloride solution, a remarkably distinct increase in the serum calcium

content was noted. In 2 cases of rabbit, the increment was from 13.56 mg/dl to 25.00 mg/dl and from 13.35 mg/dl to 22.68 mg/dl after 15 minutes respectively, and they were 26.07 mg/dl and 23.10 mg/dl after 75 minutes.

When 10 cc. per kg. of 5% calcium chloride solution was administered as enema, the serum calcium content did not demonstrate any remarkable changes, though a slight increase was noted after 15 minutes and 75 minutes, and it recovered normal value after 210 minutes.

With 10 cc. per kg. of 5% calcium sulfate solution administered as enema, no significant changes were noted in the serum calcium content.

On the calcium absorption under anesthetic condition under urethane anesthesia (Table II).

TABLE I

On the Calcium Absorption under Non-anesthetic Condition

Rabbit No. sex	Weight (kg.)	Room temperature (°C)	Substances administered and dosage	Methods of administration and pH	Time (min.)	Serum calcium content (mg/dl)	
					N	14.60	14.26
No. 1 ♀	2.200	14.0	5% Calcium chloride 20 cc. per kg.	O.A.	15	15.92	17.80
					75	17.38	15.26
No. 2 ♂	1.700			6.2	210	14.62	14.41
					24h	11.44	14.20
					N	13.56	13.35
No. 3 ♂	2.000	13.5	5% Calcium chloride 20 cc. per kg.	D.I.	15	25.00	22.68
					75	26.07	23.10
No. 4 ♂	1.800	14.5		6.1	210	15.26	16.92
					24h	10.60	11.23
					N	13.14	14.04
No. 5 ♀	2.100	14.5	5% Calcium chloride 10 cc. per kg.	E.	15	15.47	17.17
					75	14.41	16.20
No. 6 ♂	1.900	14.0		6.1	210	13.14	14.41
					24h	11.44	13.56
					N	16.63	16.20
No. 101 ♀	2.000	27.5	5% Calcium sulfate 10 cc. per kg.	E.	15	17.06	17.28
					75	15.55	15.55
No. 102 ♂	2.200			5.9	210	15.55	15.33
					24h	15.33	14.68

O.A. = Oral administration.
D.I. = Duodenal infusion.
E. = Enema.

Rabbits were given subcutaneous injections of 1 g. per kg. of urethane dissolved in 10 cc. of distilled water, and calcium solutions were administered as enema, orally or as duodenal infusion 30 minutes after the injection. Approximately 10 minutes from the injection, rabbits were lying in lateral position, and they were found completely collapsed after 30 minutes.

When 20 cc. per kg. of 5% calcium chloride solution was administered orally, the serum calcium content demonstrated a slight increase after 15 and 75 minutes, but no significant difference was noted from control cases.

With duodenal infusion of the same amount of the same solution, the serum calcium content was found distinctly increased. In 3 cases of rabbit, the serum calcium content was 23.35 mg/dl, 22.68 mg/dl and 22.68 mg/dl respectively after 15 minutes, and 25.44 mg/dl, 27.77 mg/dl and 23.74 mg/dl respectively after 75 minutes. Rabbit No. 10 became fatal with intoxication symptoms. However, when compared with the results of control tests, there were no difference between them.

When 10 cc. per kg. of 5% calcium chloride solution was administered as enema, the serum calcium content was found increased only slightly after 15 and 75 minutes similarly to the control tests.

Also in the case with 10 cc. per kg. of 5% calcium sulfate solution administered as enema, the serum calcium content did not show remarka-

TABLE II

On the Calcium Absorption under Urethane Anesthesia

Rabbit No. sex	Weight (kg.)	Dose of urethane	Room temperature (°C)	Substances administered and dosage	Methods of administration and pH	Time (min.)	Serum calcium content (mg/dl)	
No. 7 ♀	1.900	1 g. per kg.	14.0	5% Calcium chloride 20 cc. per kg.	O.A.	N	13.35	11.44
						15	15.47	11.87
						75	15.90	13.99
No. 8 ♂	2.200		14.5		6.2	210	13.35	12.50
						24h	12.93	11.23
No. 9 ♂	2.000	"	13.5	5% Calcium chloride 20 cc. per kg.	D.I.	N	12.72	13.35
						15	23.35	22.68
						75	25.44	27.77
No. 10 ♂	2.000				6.2	210	18.86	Died
						24h	13.78	
No. 11 ♂	2.000	"	14.0	5% Calcium chloride 20 cc. per kg.	D.I.	N	14.41	
						15	22.68	
						75	23.74	
					6.2	210	16.32	
						24h	13.35	
No. 107 ♀	2.100	"	14.5	5% Calcium chloride 10 cc. per kg.	E.	N	13.78	12.93
						15	14.83	14.41
						75	14.04	13.78
No. 108 ♀	2.200		14.0		6.1	210	13.78	12.72
						24h	12.50	11.44
No. 109 ♀	2.000	"	27.0	5% Calcium sulfate 10 cc. per kg.	E.	N	15.55	
						15	16.63	
						75	15.33	
					5.8	210	15.12	
						24h	14.41	

ble change, and no remarkable difference was noted between the control tests.

Under chloral hydrate anesthesia (*Table III*).

In this experiment, requisite amount of chloral hydrate was dissolved in 2.5 cc. per kg. of distilled water to be injected subcutaneously. Rabbits were administered with 10 cc. per kg. of 5% calcium chloride or calcium sulfate as enema 30 minutes after the injection.

When 0.25 g. per kg. of chloral hydrate was applied, a slight increase in the serum calcium content was recognized in Rabbit No. 13, but no remarkable change was noticed and no significant difference was noted in the case of Rabbit No. 12. Calcium absorption in the large intestine was not particularly enhanced even with an increased amount of chloral hydrate up to 0.4 g. per kg. When the amount of chloral hydrate was further increased to 0.5 g. per kg., Rabbit No. 17 and Rabbit No. 16 became fatal after 15 minutes and 210 minutes respectively, and their serum calcium content was showing a tendency of slight increase at the time of death.

When 10 cc. per kg. of 5% calcium sulfate solution was administered as enema after 0.4 g. per kg. of chloral hydrate had been given, no remarkable change in the serum calcium content was seen demonstrating no particular enhancement of calcium absorption.

Under magnesium sulfate anesthesia (*Table IV*).

Also in this experiment, a requisite amount of magnesium sulfate was dissolved in 2.5 cc. per kg. of distilled water to be injected subcutaneously. Rabbits were administered with 10 cc. per kg. of 5% calcium chloride or calcium sulfate solution as enema 30 minutes after the injection.

In the first place, 5% calcium chloride solution was administered as enema after 0.1 g. per kg. of magnesium sulfate had been applied. In this case, however, almost no change was observed in the serum calcium content, and no calcium absorption was observed even at the room temperature of 22°C. When the amount of magnesium sulfate was increased to 0.3 g. per kg., the result was found similar to that of the control tests showing no remarkable change in the serum calcium content, consequently no calcium absorption in the large intestine was observed. When the amount of magnesium sulfate was further increased to 0.5 g. per kg., the serum calcium content was found somehow increased after 15–75 minutes. However, the result cannot be regarded as any particular influence of the drug.

On the other hand, 10 cc. per kg. of 5% calcium sulfate solution was administered as enema after the preliminary treatment with 0.5 g. per kg. of magnesium sulfate. Even in this case, no increase in the serum calcium content was noted. Thus, no enhancement of calcium absorp-

TABLE III

On the Calcium Absorption under Chloral Hydrate Anesthesia

Rabbit No. sex	Weight (kg.)	Dose of chloral hydrate	Room temperature (°C)	Substances administered and dosage	Method of administration and pH	Time (min.)	Serum calcium content (mg/dl)	
No. 12 ♀	2.200	0.25g.	23.5	5% Calcium chloride 10 cc. per kg.	E.	N	13.99	13.56
						15	13.56	17.59
						75	14.62	16.96
No. 13 ♂	2.300	per kg.			6.2	210	13.14	13.35
						24h	13.14	12.72
No. 14 ♀	2.200	0.4g.	22.5	5% Calcium chloride 10 cc. per kg.	E.	N	13.99	14.41
						15	14.20	16.11
						75	17.72	14.20
No. 15 ♀	2.350	per kg.			6.1	210	13.35	13.35
						24h	12.29	13.35
No. 103 ♀	2.300	"	27.0	5% Calcium sulfate 10 cc. per kg.	E.	N	16.84	17.94
						15	17.94	18.15
						75	15.55	16.63
No. 104 ♂	2.200				5.8	210	15.76	16.20
						24h	16.20	15.76
No. 16 ♀	2.600	0.5g.	22.0	5% Calcium chloride 10 cc. per kg.	E.	N	11.23	15.05
						15	16.53	17.50
						75	17.29	Died
No. 17 ♂	2.300	per kg.			6.2	210	18.65	
						24h	Died	

tion in the large intestine induced by magnesium sulfate was recognized.

On the histamine absorption in the large intestine (*Table V*).

In the first place, when 50 mg. per kg. of histamine hydrochloride alone was dissolved in 10 cc. per kg. of distilled water and was administered as enema, the blood histamine content was 0.8 γ/cc after 30 minutes, which is approximately equal to the normal blood histamine content of rabbit.

In the case with the combined enema of 50 mg. per kg. of histamine hydrochloride and 0.3 g. per kg. of chloral hydrate, the blood histamine content was found suddenly increased to 7.2 γ/cc after 30 minutes, and the rabbits became fatal on the following day.

With the combined enema of 1 g. per kg. of urethane and 50 mg. per kg. of histamine, the blood histamine content suddenly increased to 3 γ/cc after 10 minutes. Vanish of motor reflex and dyspnoea were observed as early as after 5 minutes, convulsion was seen after 7 minutes and the rabbit became fatal after 10 minutes.

Unlike the case of chloral hydrate or urethane, in the case with the combined enema of 1 g. per kg. of magnesium sulfate and 50 mg. per kg. of histamine, it was learnt that the blood histamine content after 30 minutes was 0.8 γ/cc which is within the range of normal value.

TABLE IV

On the Calcium Absorption under Magnesium Sulfate Anesthesia

Rabbit No. sex	Weight (kg.)	Dose of Magnesium sulfate	Room temperature (°C)	Substances administered and dosage	Method of administration and pH	Time (min.)	Serum calcium content (mg/dl)	
						N	13.78	13.99
No. 18 ♂	2.300	0.1 g.	22.5	5% Calcium chloride 10 cc. per kg.	E.	15	13.35	13.99
						75	13.78	13.56
No. 19 ♀	2.300	per kg.			6.3	210	14.20	13.99
						24h	13.56	12.72
						N	10.81	11.44
No. 20 ♀	2.600	0.3 g.	22.5	5% Calcium chloride 10 cc. per kg.	E.	15	11.23	13.35
						75	11.23	11.66
No. 21 ♀	2.500	per kg.			6.3	210	11.02	11.44
						24h	10.81	10.81
						N	13.56	12.72
No. 22 ♂	2.000	0.5 g.	21.0	5% Calcium chloride 10 cc. per kg.	E.	15	18.23	14.44
						75	15.47	14.44
No. 23 ♀	2.100	per kg.			6.3	210	11.44	11.66
						24h	12.08	11.66
						N	12.74	14.47
No. 105 ♂	2.500			5% Calcium sulfate	E.	15	12.09	12.74
		"	31.0			75	10.58	13.14
No. 106 ♀	2.500			10 cc. per kg.	5.8	210	12.09	14.47
						24h	12.09	12.74

It was also clarified that, in the case with simple enema of chloral hydrate, urethane or magnesium sulfate respectively for the purpose of control tests, the blood histamine content remained within the range of normal value.

SUMMARY

Summarizing the results of the above experiments, it was learnt that, under urethane anesthesia, the absorption patterns of calcium are almost the same as those of under non-anesthetic condition in the cases of oral administration, duodenal infusion and enema of calcium chloride solution, and that urethane itself was considered not to have exercised any influences on the calcium absorption. Similarly to the case of urethane, under anesthetic condition with chloral hydrate or magnesium sulfate, the calcium absorption in the large intestine was not generally influenced. Kondo reported that, the combined enema with chloral hydrate enhances remarkably the calcium absorption in the large intestine, but not with magnesium sulfate. In view of the above fact, it was clarified that the calcium absorption in the large intestine is greatly influenced by the combined enema of appropriate narcotic and calcium preparation.

TABLE V

On the Histamine Absorption in the Large Intestine

Rabbit No. sex	Weight (kg.)	Room temperature (°C)	Substances administered and dosage	Method of administration and pH	Time of bleeding after histamine enema (min.)	Blood histamine content (γ/cc)
No. 167 ♀	2.100	28.0				0.9
No. 160 ♀	2.100	28.0	Histamine hydrochloride 50 mg. per kg.	E. 5.1	30	0.8
No. 161 ♀	2.200	22.0	Histamine hydrochloride 50 mg. per kg. Chloral hydrate 0.3 g. per kg.	E. 5.3	30 Fatal on the following day	7.2
No. 162 ♀	2.100	22.5	Chloral hydrate 0.3 g. per kg.	E. 6.0	30	0.8
No. 163 ♀	2.000	21.0	Histamine hydrochloride 50 mg. per kg. Magnesium sulfate 1 g. per kg.	E. 5.2	30	0.8
No. 164 ♀	2.000	21.0	Magnesium sulfate 1 g. per kg.	E. 6.1	30	1.0
No. 165 ♀	2.100	20.0	Histamine hydrochloride 50 mg. per kg. Urethane 1 g. per kg.	E. 5.3	10 Died	3.0
No. 166 ♂	2.000	20.0	Urethane 1 g. per kg.	E. 6.1	30	0.7

As regards the histamine absorption in the large intestine, on the other hand, with a simple administration of 50 mg. per kg. of histamine as enema, the blood histamine content was approximately 0.8 γ/cc, which is within the range of normal blood histamine content of rabbit (0.6–1.0 γ/cc) reported by Yokoyama, Shimazaki[12], Fukuda[13] etc. Thus, it was learnt that histamine thus administered is almost not absorbed in the large intestine. Contrary to the above, when 50 mg. per kg. of histamine hydrochloride combined with chloral hydrate or urethane is administered as enema, the blood histamine content suddenly increases, and the rabbit becomes fatal with a symptom resembling shock. However, when the same amount of histamine combined with magnesium sulfate is administered as enema, the blood histamine content remains almost within the normal range, and any enhanced histamine absorption is not noted. Reviewing the findings by Tsunoo *et al.* that the penicillin absorption in the large intestine is distinctly enhanced by the combined enema with urethane, it is very interesting to note that the histamine absorption in the large intestine

is similarly enhanced by the combined enema with urethane.

Conclusions

1. In the oral administration, duodenal infusion and enema of calcium chloride, urethane anesthesia almost does not influence the calcium absorption.

2. The anesthetic condition with 0.4 g. per kg. of chloral hydrate injected subcutaneously almost does not influence the calcium absorption in the large intestine. With 0.5 g. per 1 g. injected subcutaneously, the calcium absorption in the large intestine somehow demonstrates tendency of enhancement.

3. In the case under the anesthesia with 0.1–0.5 g. per kg. of magnesium sulfate injected subcutaneously, the calcium absorption in the large intestine is generally not influenced.

4. No histamine absorption in the large intestine is observed when 50 mg. per kg. of histamine hydrochloride is administered as enema.

5. The absorption of histamine hydrochloride in the large intestine is enhanced by urethane or chloral hydrate resulting a sudden increase of blood histamine content and intoxication death of rabbit.

6. The absorption of histamine hydrochloride in the large intestine is not influenced by magnesium sulfate.

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